



CLINICAL PROTOCOL

A PHASE 3 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY OF THE ANALGESIC EFFICACY AND SAFETY OF THE SUBCUTANEOUS ADMINISTRATION OF TANEZUMAB IN SUBJECTS WITH OSTEOARTHRITIS OF THE HIP OR KNEE

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| Original protocol | 25 August 2015 | Not Applicable (N/A) |
| Amendment 1 | 13 November 2015 | <p>Section 1.2.7. This section on Benefit-Risk Assessment was added.</p> <p>Sections 4.1, 4.2, 4.4 and 6.1.1. The text was revised concerning contraception.</p> <p>Section 5.2. Details for unblinding with an electronic system and a back-up procedure added.</p> <p>Section 5.7.1 and Appendix 3. The routes of NSAID administration were clarified. Details on the use of glucosamine sulfate and chondroitin sulfate, and duloxetine were add.</p> <p>Sections 5.8 and 6.1.2. Rescue medication was modified.</p> <p>Section 12.1. Wording for approval needed from the national competent authority before implementing a substantial amendment is added.</p> <p>Section 13.1. The section amended to specify that the end of the trial will be last patient last visit.</p> |

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| Amendment 2 Sweden and France country-specific | 10 February 2016 | <p><u>For Sweden:</u></p> <p>Sections 4.1, 4.2, 4.4, 6.1.1 and Appendix 14. Additional text was added for Sweden concerning contraception.</p> <p>Section 12.2. Additional text was added for Sweden concerning the Declaration of Helsinki.</p> <p><u>For France:</u></p> <p>Appendix 15 for contrat unique for study sites located in France.</p> |
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PROTOCOL SUMMARY

Background

Tanezumab is a monoclonal antibody that binds to and inhibits the actions of nerve growth factor (NGF). The Nerve Growth Factor Inhibitor (NGFI) class may offer an important breakthrough in the treatment of chronic pain and is under clinical investigation for the treatment of pain associated with osteoarthritis or other chronic pain conditions.¹

The completed Phase 2 and Phase 3 studies conducted to date have demonstrated that tanezumab is efficacious and generally safe and well tolerated for the treatment of pain due to osteoarthritis and chronic low back pain.

The primary objective of this study is to demonstrate superior efficacy of tanezumab 5 mg and 2.5 mg administered subcutaneously (SC) every 8 weeks versus placebo at Week 24 in subjects with osteoarthritis of the knee or hip. The 2.5 mg dose was shown to provide efficacy benefits with a favorable safety profile when administered intravenously in previous Phase 3 clinical trials. The 5 mg dose is expected to provide added efficacy benefit over the 2.5 mg dose based on data from previous studies.

OBJECTIVES AND ENDPOINTS

Primary Objective

- Demonstrate superior efficacy of tanezumab 5 mg and 2.5 mg administered subcutaneously (SC) every 8 weeks versus placebo at Week 24.

SECONDARY OBJECTIVE

- Evaluate the safety of tanezumab 2.5 mg SC and 5 mg SC.

PRIMARY ENDPOINTS

The co-primary efficacy endpoints are:

- Change from Baseline to Week 24 in the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) Pain subscale;
- Change from Baseline to Week 24 in the WOMAC Physical Function subscale;
- Change from Baseline to Week 24 in the Patient's Global Assessment of Osteoarthritis.

SECONDARY ENDPOINTS

Efficacy Measures

- WOMAC Pain subscale change from Baseline to Weeks 2, 4, 8, 12, 16, and 32.
- WOMAC Physical Function subscale change from Baseline to Weeks 2, 4, 8, 12, 16, and 32.

- Patient's Global Assessment of Osteoarthritis (5 point Likert scale) change from Baseline to Weeks 2, 4, 8, 12, 16, and 32.
- Outcome Measures in Rheumatology – Osteoarthritis Research Society Initiative (OMERACT-OARSI) responder index at Weeks 2, 4, 8, 12, 16, 24, and 32.
- Cumulative distribution of percent change from Baseline in the WOMAC Pain subscale score to Week 16 and 24 (endpoint for summary only).
- Treatment Response: Reduction in the WOMAC Pain subscale of $\geq 30\%$, $\geq 50\%$, $\geq 70\%$ and $\geq 90\%$, at Weeks 2, 4, 8, 12, 16, 24, and 32.
- Treatment Response: Reduction in the WOMAC Physical Function subscale of $\geq 30\%$, $\geq 50\%$, $\geq 70\%$ and $\geq 90\%$ at Weeks 2, 4, 8, 12, 16, 24, and 32.
- Cumulative distribution of percent change from Baseline in the WOMAC Physical Function subscale score to Week 16 and 24 (endpoint for summary only).
- Treatment Response: Improvement of ≥ 2 points in Patient's Global Assessment of Osteoarthritis at Weeks 2, 4, 8, 12, 16, 24, and 32.
- Average pain score in the index knee or hip change from Baseline to Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 28 and 32.
- WOMAC Stiffness subscale change from Baseline to Weeks 2, 4, 8, 12, 16, 24 and 32.
- WOMAC Average score change from Baseline to Weeks 2, 4, 8, 12, 16, 24, and 32.
- WOMAC Pain Subscale Item: Pain When Walking on a Flat Surface, change from Baseline to Weeks 2, 4, 8, 12, 16, 24, and 32.
- WOMAC Pain Subscale Item: Pain When Going Up or Downstairs, change from Baseline to Weeks 2, 4, 8, 12, 16, 24, and 32.
- Work Productivity and Activity Impairment Questionnaire for Osteoarthritis (WPAI:OA) impairment scores change from Baseline to Weeks 8, 16 and 24.
- EQ-5D-5L Health State Utility and Five Items (Mobility; Self-Care; Usual Activities; Pain/Discomfort; Anxiety/Depression) change from Baseline to Weeks 8, 16 and 24.
- Patient Reported Treatment Impact Assessment-Modified (mPRTI) at Weeks 16 and 24.
- Health Care Resource Utilization at Baseline, and Weeks 32 and 48.
- Incidence and time to discontinuation due to Lack of Efficacy.

- Usage of rescue medication (incidence and number of days of use) during Weeks 2, 4, 8, 12, 16, 24, and 32.
- Usage of rescue medication (amount taken) during Weeks 2, 4, 8, 12, 16 and 24.

Safety Measures

- Adverse Events.
- Standard safety assessments (safety laboratory testing [chemistry, hematology], sitting vital signs, electrocardiogram (ECG; 12-lead).
- Joint Safety Adjudication outcomes.
- Total joint replacements.
- Orthostatic (supine / standing) blood pressure assessments.
- Survey of Autonomic Symptom scores.
- Neurologic exam (Neuropathy Impairment Score [NIS]).
- Anti-tanezumab antibody assessments.
- Physical examinations.

Tertiary Endpoints

Pharmacokinetic and Pharmacodynamic

- Plasma tanezumab concentrations.
- Serum NGF concentrations.
- Serum and urine osteoarthritis biomarker concentrations.

STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, parallel-group multicenter study of the efficacy and safety of tanezumab when administered by SC injection for 24 weeks compared to placebo in subjects with osteoarthritis of the knee or hip. Approximately 810 subjects will be randomized to 1 of 3 treatment groups in a 1:1:1 ratio (ie, 270/group). Subjects will receive three SC injections of one of the following treatments at an 8-week interval:

1. tanezumab 2.5 mg;
2. tanezumab 5 mg;

3. Placebo to match tanezumab.

The study is designed with a total post-randomization duration of 48 weeks and will consist of three periods: Screening (up to 37 days), Double-blind Treatment (24 weeks) and Safety Follow-up (24 weeks). The Screening period (beginning up to 37 days prior to Randomization) includes a Washout Period (lasting a minimum of 2 days), if required, and an Initial Pain Assessment Period (the 7 days prior to Baseline [Day 1]).

STATISTICAL METHODS

Sample Size Determination

A sample size of 270 subjects per treatment group is needed to provide approximately 80% power to achieve statistical significance (at the 5% two-sided level) for the two comparisons of tanezumab 2.5 and 5 mg SC versus placebo, over all three co-primary endpoints. The total sample size will be approximately 810 subjects.

PRIMARY ANALYSIS

The co-primary efficacy endpoints will be analyzed using an analysis of covariance (ANCOVA) model, with model terms for Baseline score, Baseline Diary Average Pain, index joint (knee or hip), highest Kellgren-Lawrence grade, and treatment group, and study site as a random effect. The assessment of significance for the tanezumab SC versus placebo treatment contrasts will use a step-down testing strategy within each of the co-primary efficacy endpoints defined as first testing tanezumab 5 mg versus placebo, and if statistically significant ($p \leq 0.05$) to then test tanezumab 2.5 mg versus placebo. Finally, a tanezumab treatment group is declared as superior to placebo if the corresponding treatment contrast is significant over all three co-primary endpoints. This testing procedure will maintain the Type I error to 5% or less within each of the co-primary efficacy endpoints, and to less than 5% for all three co-primary efficacy endpoints. An additional (main effects ANCOVA) analysis for each of the co-primary efficacy endpoints will use a per-protocol analysis set, which will exclude subjects who are major protocol deviators.

The primary analysis of the co-primary endpoints will use multiple imputations for missing data, to account for uncertainty around the subject response. The basis for imputing missing values will be dependent on the reasons for missing data. For subjects with missing data due to discontinuation prior to Week 24 for lack of efficacy or for an adverse event or death, imputation will be based on sampling from a normal distribution using a mean value equal to the subject's Baseline efficacy value and the standard deviation (over all treatment groups) of the observed efficacy data at Week 24. For subjects with missing data for any other reason, imputation will be based on sampling from a normal distribution using a mean value equal to the subject's last observed efficacy value and standard deviation (over all treatment groups) of the observed efficacy data at Week 24. One hundred imputation samples will be used, and the ANCOVA model described above will be used for each imputation dataset. The final results will be calculated using the combined sets of results from each imputation dataset analysis.²

DATA MONITORING COMMITTEE

An independent, external Data Monitoring Committee (E-DMC) has been instituted for the tanezumab clinical program. This committee will be composed of at least one rheumatologist, neurologist, statistician, and epidemiologist. The E-DMC will review unblinded safety data including (but not limited to) adverse events and serious adverse events on a regular basis throughout the trial. The E-DMC will have written operating procedures and a Charter, including a specific description of the scope of their responsibilities.

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Table 1. SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to [Study Procedures](#) and [Assessments](#) sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the subject.

| Study Activities Visit Identifier | Screening ^b Day -37 to Day -1 | | | Double-Blind Treatment | | | | | | | End of Treat- ment | Safety Follow-Up ^o | | |
|---|---|----------------------------------|--|---------------------------|---------------------------|---------------------------|---------------------------|------------------------|----------------------------|----------------------------|--------------------------|--|--|---------------------------------|
| | | | | | | | | | | | | 16 weeks post last dose Visit | Phone Calls ^r | End of Study/ Final visit |
| | Clinic visits | Phone call ^r | Week 24 | Week 32 | Weeks 28, 36, 40, 44 | Week 48 | | | | | | | | |
| | Initial screen | Was hout and X- rays | Initial Pain Assess- ment Period | Base line ^c | Week 2 | Week 4 | Week 8 ^c | Week 12 | Week 16 ^c | Week 20 ^r | | | | |
| Visit Window ^a | | | Day -7 to Day -1 | Day 1 | Day 15 (±3 days) | Day 29 (±3 days) | Day 57 (±7 days) | Day 85 (±7 days) | Day 113 (±7 days) | Day 141 (±7 days) | Day 169 (±7 days) | Day 225 (±7 days) | Days 197, 253, 281, 309 (±7 days) | Day 337 (±7 days) |
| Informed Consent | X | | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | | | X | | | | | | | | | | |
| General and Musculoskeletal Specific Medical History and Prior/Current Medication Use ^d | X | | | | | | | | | | | | | |
| Primary Diagnosis/ Demographics | X | | | | | | | | | | | | | |
| Weight/Height/BMI/Smoking Status/Female Hormonal Status/Alcohol Use | X | | | | | | | | | | X ^e | | | |
| General Physical Examination | X | | | | | | | | | | X | | | |
| Musculoskeletal Assessment ^f | X | | | X | X | X | X | X | X | | X | X | | X |

| Study Activities Visit Identifier | Screening ^b Day -37 to Day -1 | | | Double-Blind Treatment | | | | | | | End of Treat- ment | Safety Follow-Up ^o | | |
|---|---|----------------------------------|---|---------------------------|---------------------------|---------------------------|---------------------------|----------------------------|----------------------------|----------------------------|--------------------------|--|--|---------------------------------|
| | | | | | | | | | | | | 16 weeks post last dose Visit | Phone Calls ^r | End of Study/ Final visit |
| | Clinic visits | | | | | | | Phone call ^r | Week 24 | Week 32 | | Weeks 28, 36, 40, 44 | Week 48 | |
| | Initial screen | Was hout and X- rays | Initial Pain Assess ment Period | Base line ^c | Week 2 | Week 4 | Week 8 ^c | Week 12 | Week 16 ^c | Week 20 ^r | | | | |
| Visit Window ^a | | | Day -7 to Day -1 | Day 1 | Day 15 (±3 days) | Day 29 (±3 days) | Day 57 (±7 days) | Day 85 (±7 days) | Day 113 (±7 days) | Day 141 (±7 days) | Day 169 (±7 days) | Day 225 (±7 days) | Days 197, 253, 281, 309 (±7 days) | Day 337 (±7 days) |
| Radiograph Assessment of Hips, Knees and Shoulders | X | | | | | | | | | | X | | | X |
| Neurologic Exam Neuropathy Impairment Score (NIS) ^g | X | | | X | X | X | X | X | X | | X | X | | X |
| Sitting Vital Signs (BP, HR), and orthostatic BP testing | X | | | X | X | X | X | X | X | | X | X | | X |
| Survey of Autonomic Symptoms (SAS) questionnaire ⁱ | X | | | | | | | | | | X | | | |
| Electrocardiogram (ECG 12-lead) | X | | | | | | | | | | X | | | X |
| Laboratory | | | | | | | | | | | | | | |
| Hepatitis Screen (Hepatitis B & Hepatitis C); HIV test, Urine Toxicology screen | X | | | | | | | | | | | | | |
| Hemoglobin A1c | X | | | | | | | | | | | | | |
| Serum FSH Test ^h | X | | | | | | | | | | | | | |
| Serum/Urine Pregnancy Test ^p | X | | | X | | | X | | X | | X | X | | |
| Hematology | X | | | X | | | | | X | | | X | | |
| Blood Chemistry | X | | | X | | | | | X | | | X | | |
| Urinalysis | X | | | | | | | | | | | | | |
| Serum and Plasma Retention Samples | | | | X | | | | | | | X | X | | |

| Study Activities Visit Identifier | Screening ^b Day -37 to Day -1 | | | Double-Blind Treatment | | | | | | | End of Treatment | Safety Follow-Up ^o | | |
|---|---|---------------------|---|------------------------|------------------|------------------|---------------------|------------------|----------------------|----------------------|-------------------|---|-----------------------------------|------------------------------|
| | | | | | | | | | | | | 16 weeks post last dose Visit | Phone Calls ^r | End of Study/ Final visit |
| | Initial screen | Was hout and X-rays | Initial Pain Assessment Period | Base line ^c | Week 2 | Week 4 | Week 8 ^c | Week 12 | Week 16 ^c | Week 20 ^r | Week 24 | Week 32 | Weeks 28, 36, 40, 44 | Week 48 |
| Visit Window ^a | | | Day -7 to Day -1 | Day 1 | Day 15 (±3 days) | Day 29 (±3 days) | Day 57 (±7 days) | Day 85 (±7 days) | Day 113 (±7 days) | Day 141 (±7 days) | Day 169 (±7 days) | Day 225 (±7 days) | Days 197, 253, 281, 309 (±7 days) | Day 337 (±7 days) |
| Plasma Pharmacokinetic sample ⁱ | | | | X | | | X | | X | | X | X | | X |
| Serum NGF ^l | | | | X | | | X | | | | X | X | | X |
| Serum Anti-Drug Antibody ^l | | | | X | | | X | | X | | X | X | | X |
| Serum and Urine Biomarkers ^l | | | | X | | | X | | | | | | | |
| Banked biospecimen (whole blood) | | | | X | | | | | | | | | | |
| Washout | | | | | | | | | | | | | | |
| Discontinue Current Pain Medication | X | | | | | | | | | | | | | |
| Subject Daily/Weekly Assessments (IRT)^k | | | | | | | | | | | | | | |
| Numeric Pain Scale Rating | (X) | (X) |Daily Entries for Index Joint and Weekly For Non-index Joints..... | | | | | | | | | Weekly Entries for Index and Non-index Joints | | |
| Rescue Medication Use | (X) | (X) |Daily entries..... | | | | | | | | | Weekly entries | | |
| Concomitant NSAID Use | | | | | | | | | | | | Weekly Entries | | |
| Randomization | | | | X | | | | | | | | | | |
| Study Treatment | | | | | | | | | | | | | | |
| SC Investigational Product | | | | X | | | X | | X | | | | | |
| Subject Reported Assessments Completed at Study Visits^l | | | | | | | | | | | | | | |
| WOMAC Pain Subscale | X | | | X | X | X | X | X | X | | X | X | | |
| WOMAC Physical Function and Stiffness Subscales | | | | X | X | X | X | X | X | | X | X | | |

| Study Activities Visit Identifier | Screening ^b Day -37 to Day -1 | | | Double-Blind Treatment | | | | | | | End of Treatment | Safety Follow-Up ^o | | |
|---|---|---------------------|---------------------------------|------------------------|------------------|------------------|---------------------|-------------------------|----------------------|----------------------|-------------------|-------------------------------|-----------------------------------|------------------------------|
| | | | | | | | | | | | | 16 weeks post last dose Visit | Phone Calls ^r | End of Study/ Final visit |
| | Clinic visits | | | | | | | Phone call ^r | Week 24 | Week 32 | | Weeks 28, 36, 40, 44 | Week 48 | |
| | Initial screen | Was hout and X-rays | Initial Pain Assess ment Period | Base line ^c | Week 2 | Week 4 | Week 8 ^c | Week 12 | Week 16 ^c | Week 20 ^r | | | | |
| Visit Window ^a | | | Day -7 to Day -1 | Day 1 | Day 15 (±3 days) | Day 29 (±3 days) | Day 57 (±7 days) | Day 85 (±7 days) | Day 113 (±7 days) | Day 141 (±7 days) | Day 169 (±7 days) | Day 225 (±7 days) | Days 197, 253, 281, 309 (±7 days) | Day 337 (±7 days) |
| Patient Global Assessment of Osteoarthritis | | | | X | X | X | X | X | X | | X | X | | |
| WPAI:OA | | | | X | | | X | | X | | X | | | |
| EQ-5D-5L | | | | X | | | X | | X | | X | | | |
| mPRTI | | | | | | | | | X | | X | | | |
| Health Care Resource Utilization Assessment (HCRU) | | | | X | | | | | | | | X | | X |
| Other Assessments/Procedures Conducted at Study Visits | | | | | | | | | | | | | | |
| Adverse event assessment | | | | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medication review | | | | X | X | X | X | X | X | X | X | X | X | X |
| Review compliance with subject IRT entry ^q | X | | | X | X | X | X | X | X | X | X | X | X | |
| Rescue medication return/compliance ^m | | | | X | X | X | X | X | X | | X | X | | |
| Dispense rescue medication | X | | | X | X | X | X | X | X | | X | | | |
| Assign standard of care treatment as needed ⁿ | | | | | | | | | | | | X | | |
| Female Subjects of Childbearing Potential Reminded of Contraceptive Requirements ^s | X | X | X | X | X | X | X | X | X | X | X | X | X (Week 28 only) | |

| Study Activities Visit Identifier | Screening ^b Day -37 to Day -1 | | | Double-Blind Treatment | | | | | | | End of Treat- ment | Safety Follow-Up ^o | | |
|-----------------------------------|---|----------------------------------|---|---------------------------|---------------------------|---------------------------|---------------------------|------------------------|----------------------------|----------------------------|--------------------------|--|--|---------------------------------|
| | | | | | | | | | | | | 16 weeks post last dose Visit | Phone Calls ^r | End of Study/ Final visit |
| | Initial screen | Was hout and X- rays | Initial Pain Assess- ment Period | Base line ^c | Week 2 | Week 4 | Week 8 ^c | Week 12 | Week 16 ^c | Week 20 ^r | Week 24 | Week 32 | Weeks 28, 36, 40, 44 | Week 48 |
| Visit Window ^a | | | Day -7 to Day -1 | Day 1 | Day 15 (±3 days) | Day 29 (±3 days) | Day 57 (±7 days) | Day 85 (±7 days) | Day 113 (±7 days) | Day 141 (±7 days) | Day 169 (±7 days) | Day 225 (±7 days) | Days 197, 253, 281, 309 (±7 days) | Day 337 (±7 days) |

Abbreviations: BP = Blood Pressure; ECG = electrocardiogram; HR = Heart Rate; HCRU = Health Care Resource Utilization; EC = ethics committee; EQ-5D-5L = EuroQol 5 Dimension; IRT = Interactive Response Technology; mPRTI = Patient Reported Treatment Impact assessment-modified; NGF = Nerve Growth Factor; NIS = Neuropathy Impairment Score; NSAID = Non-Steroidal Anti-Inflammatory Drug; PD = Pharmacodynamics; SAS = Survey of Autonomic Symptoms; WPAI: OA = Work Productivity and Activity Impairment Questionnaire: Osteoarthritis; BMI = Body Mass Index; HIV = Human Immunodeficiency Virus; FSH = Follicle-Stimulating Hormone; SC = Sub-Cutaneous; WOMAC = Western Ontario and McMaster University Osteoarthritis Index.


| Study Activities Visit Identifier | Screening ^b Day -37 to Day -1 | | | Double-Blind Treatment | | | | | | | End of Treatment | Safety Follow-Up ^o | | |
|-----------------------------------|---|---------------------|---------------------------------|------------------------|------------------|------------------|---------------------|-------------------------|----------------------|----------------------|-------------------|-------------------------------|-----------------------------------|------------------------------|
| | | | | | | | | | | | | 16 weeks post last dose Visit | Phone Calls ^r | End of Study/ Final visit |
| | Clinic visits | | | | | | | Phone call ^r | Week 24 | Week 32 | | Weeks 28, 36, 40, 44 | Week 48 | |
| | Initial screen | Was hout and X-rays | Initial Pain Assess ment Period | Base line ^c | Week 2 | Week 4 | Week 8 ^c | Week 12 | Week 16 ^c | Week 20 ^r | | | | |
| Visit Window ^a | | | Day -7 to Day -1 | Day 1 | Day 15 (±3 days) | Day 29 (±3 days) | Day 57 (±7 days) | Day 85 (±7 days) | Day 113 (±7 days) | Day 141 (±7 days) | Day 169 (±7 days) | Day 225 (±7 days) | Days 197, 253, 281, 309 (±7 days) | Day 337 (±7 days) |

- a. Day relative to start of study treatment (Day 1).
- b. The Screening period begins up to a maximum of 37 days prior to randomization. Prior to entering the IPAP, subjects must washout from prohibited pain medications for at least 5 half-lives or 48 hrs (whichever is greater). During the IPAP, diary entries (joint pain and rescue medication use) must be provided for a minimum of 3 days in the 7 days immediately preceding randomization.
- c. All study activities at dosing visits (Baseline [Day 1] and Weeks 8 and 16), including sample collection, are performed prior to dosing, unless otherwise noted.
- d. At Screening, a comprehensive musculoskeletal medical history is obtained; see [Section 7.3.1.2](#) for details. History of insufficient pain relief from, inability to tolerate or contraindication to take acetaminophen, NSAIDs and tramadol or opioids should be collected. All treatments used to treat osteoarthritis and osteoarthritis pain and reasons for discontinuing should also be collected.
- e. Only body weight is collected at Week 24 (End of Treatment).
- f. A musculoskeletal directed physical examination will be performed at each clinic visit; findings will be recorded on a case report form and findings of worsening clinical status considered clinically significant will be reported as adverse events. This physical examination is described in [Section 7.3.1.2](#).
- g. A neurological examination (NIS) will be performed by the Investigator (or designated physician) at each clinic visit and assessed for clinically significant changes from Baseline. Requirements for neurological consultation at which a full neurological examination is to be performed by a neurologist are detailed in [Section 7.3.8](#).
- h. FSH testing in female subjects as described in [Section 7.3.2.4](#).
- i. On dosing visits, samples for ADA, PK and NGF should be obtained pre-dose.
- j. Biomarker samples should be collected pre-dose at approximately the same time of the day at all scheduled time points and as much as possible following a fasting period of at least 8 hours. Fasting status should be recorded on the eCRF. Urine collected for biomarkers should be the second or later void of the day.
- k. IRT: interactive response technology. For the index joint, pain scores are collected daily from the beginning of the IPAP to Week 24 (End of Treatment visit) though collection may start as early as at the Screening Visit, and then weekly from Week 24 to Week 48. For non-index joints, pain assessments are collected weekly from the IPAP to Week 48 (End of Study visit) with a 24-hour recall. Rescue medication use is collected daily from the beginning of the IPAP to Week 24 (End of Treatment visit) though collection may start as early as at the Screening Visit; then weekly from Week 24 to Week 48. Concomitant NSAID use is collected weekly from Baseline to Week 48 via IRT. Compliance with IRT assessments is to be reviewed at each study visit, including at telephone visits.
- l. The WOMAC subscales, PGA of Osteoarthritis, WPAI:OA and EQ-5D-5L, HCRU and SAS will be administered at sites using IRT.

| Study Activities Visit Identifier | Screening ^b Day -37 to Day -1 | | | Double-Blind Treatment | | | | | | | End of Treat- ment | Safety Follow-Up ^o | | |
|-----------------------------------|---|----------------------------------|---|---------------------------|---------------------------|---------------------------|---------------------------|----------------------------|----------------------------|----------------------------|--------------------------|--|--|---------------------------------|
| | | | | | | | | | | | | 16 weeks post last dose Visit | Phone Calls ^r | End of Study/ Final visit |
| | Clinic visits | | | | | | | Phone call ^r | | | | | | |
| | Initial screen | Was hout and X- rays | Initial Pain Assess ment Period | Base line ^c | Week 2 | Week 4 | Week 8 ^c | Week 12 | Week 16 ^c | Week 20 ^r | Week 24 | Week 32 | Weeks 28, 36, 40, 44 | Week 48 |
| Visit Window ^a | | | Day -7 to Day -1 | Day 1 | Day 15 (±3 days) | Day 29 (±3 days) | Day 57 (±7 days) | Day 85 (±7 days) | Day 113 (±7 days) | Day 141 (±7 days) | Day 169 (±7 days) | Day 225 (±7 days) | Days 197, 253, 281, 309 (±7 days) | Day 337 (±7 days) |

- ^{m.} Rescue medication use must be discontinued 24 hours prior to any on site study visit up to and including Week 32 (including during the Early Termination Follow-Up period). Subjects should bring back rescue medication bottles at each study visit for assessment of compliance.
- ^{n.} If needed, following completion of the visit at which final efficacy assessments are collected (Week 32, 16 weeks after the last dose of investigational product administered), standard of care treatment (as described in [Section 6.3.2.](#)) may be initiated, and usage recorded on the concomitant medication CRF.
- ^{o.} Subjects discontinuing the study at their request or at the decision of the investigator prior to Week 24 should be withdrawn from treatment and begin the 24-week Early Termination Follow-Up period described in [Section 6.4](#) and [Table 2](#). The follow-up period for subjects who terminate early includes 3 clinic visits and 2 telephone visits as described in [Section 6.4.1](#). Subjects who undergo joint replacement will be followed for 24 weeks after the procedure as described in [Section 6.4.2](#).
- ^{p.} Serum pregnancy tests are obtained at Screening, Weeks 24 and 32 or Early Termination Visits 1 and 2 for subjects who discontinue (Refer to [Section 6.4](#)). A urine pregnancy test will be obtained and confirmed as negative prior to dosing at Baseline before initial dosing, and at Weeks 8 and 16. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.
- ^{q.} Subject Daily / Weekly Assessments (IRT) - Compliance with IRT assessments is to be reviewed at each study visit, including telephone visits.
- ^{r.} Week 20, 28, 36, 40 and 44 Visits are made by telephone call.
- ^{s.} During Washout and Initial Pain Assessment Periods, contraceptive requirement reminders may be done by telephone contact.

Table 2. EARLY TERMINATION SCHEDULE OF EVENTS

| Visit Identifier | As soon as possible after determining subject will be discontinued from study | Early Termination Visit 1 | Early Termination Telephone Contact 1 | Early Termination Visit 2 | Early Termination Telephone Contact 2 | Early Termination Visit 3 |
|--|--|-----------------------------|---------------------------------------|------------------------------|---------------------------------------|------------------------------|
| | | ~8 Weeks after last SC dose | ~12 Weeks after last SC dose | ~16 Weeks after last SC dose | ~20 Weeks after last SC dose | ~24 Weeks after last SC dose |
| Radiographs of each Hip, Knee and Shoulder | X | | | | | X |
| General Physical Examination | | X | | | | |
| Musculoskeletal Physical Examination ^a | | X | | X | | X |
| Vital Signs (BP, HR) | | X | | X | | X |
| Orthostatic Blood Pressure (supine/standing) | | X | | X | | X |
| Body Weight | | X | | | | |
| Electrocardiogram (ECG 12-lead) | | X | | | | X |
| Survey of Autonomic Symptoms (SAS) questionnaire ^b | | X | | | | X |
| Neurologic Exam Neuropathy Impairment Score (NIS) ^c | | X | | X | | X |
| Subject Weekly Assessments (IRT) ^d |  | | | | | |
| Review Compliance With Subject IRT Entry and Data Review ^d | | X | X | X | X | X |
| Adverse Event Assessment | | X | X | X | X | X |
| Female Subjects of Childbearing Potential Reminded of Contraceptive Requirements | | X | X | X | | |

| Visit Identifier | As soon as possible after determining subject will be discontinued from study | Early Termination Visit 1 | Early Termination Telephone Contact 1 | Early Termination Visit 2 | Early Termination Telephone Contact 2 | Early Termination Visit 3 |
|---|---|-----------------------------|---------------------------------------|------------------------------|---------------------------------------|------------------------------|
| | | ~8 Weeks after last SC dose | ~12 Weeks after last SC dose | ~16 Weeks after last SC dose | ~20 Weeks after last SC dose | ~24 Weeks after last SC dose |
| SUBJECT REPORTED ASSESSMENTS (Completed at Study Visits)^b | | | | | | |
| WOMAC Pain, Physical Function and Stiffness Subscales | | X | | X | | |
| Patient's Global Assessment of Osteoarthritis | | X | | X | | |
| WPAI:OA | | X | | X | | |
| EQ-5D-5L | | X | | X | | |
| mPRTI | | X | | | | |
| Health Care Resource Utilization (HCRU) | | | | X | | X |
| RESCUE MEDICATION / STANDARD OF CARE | | | | | | |
| Concomitant Medication Review | | X | X | X | X | X |
| Rescue medication return/compliance ^e | | X | | X | | |
| Assign Standard of Care Treatment as Needed ^f | | | | X | | |
| LABORATORY | | | | | | |
| Serum Pregnancy Test ^g | | X | | X | | |
| Hematology | | | | X | | |
| Blood Chemistry | | | | X | | |
| Serum and Plasma Retention Samples | | X | | X | | |
| Serum Anti-tanezumab Antibody | | X | | X | | X |
| Plasma Pharmacokinetic sample | | X | | X | | |
| Serum NGF (PD) sample | | X | | X | | |
| Serum and Urine Biomarkers ^h | | X | | | | |

Abbreviations: → = ongoing/continuous event; BP = Blood Pressure; ECG = electrocardiogram; HR = Heart Rate; HCRU = Health Care Resource Utilization; EC = ethics committee; EQ-5D-5L = EuroQol 5 Dimension; IRT = Interactive Response Technology; mPRTI = Patient Reported Treatment Impact assessment-modified; NGF = Nerve Growth Factor; NIS = Neuropathy Impairment Score; PD = Pharmacodynamics; SAS = Survey of Autonomic Symptoms; SC = Sub-Cutaneous; WPAI: OA = Work Productivity and Activity Impairment Questionnaire; WOMAC = Western Ontario and McMaster University Osteoarthritis Index.

| Visit Identifier | As soon as possible after determining subject will be discontinued from study | Early Termination Visit 1 | Early Termination Telephone Contact 1 | Early Termination Visit 2 | Early Termination Telephone Contact 2 | Early Termination Visit 3 |
|------------------|---|-----------------------------|---------------------------------------|------------------------------|---------------------------------------|------------------------------|
| | | ~8 Weeks after last SC dose | ~12 Weeks after last SC dose | ~16 Weeks after last SC dose | ~20 Weeks after last SC dose | ~24 Weeks after last SC dose |

- ^a A musculoskeletal directed physical examination will be performed at each clinic visit; findings will be recorded on a case report form and findings of worsening clinical status considered clinically significant will be reported as adverse events. This physical examination is described in [Section 7.3.1.2](#).
- ^b The WOMAC subscales, PGA of Osteoarthritis, WPAI:OA and EQ-5D-5L, HCRU and SAS will be administered at sites using IRT.
- ^c A neurological examination (NIS) will be performed by the Investigator (or designated physician) at each clinic visit and assessed for clinically significant changes from Baseline. Requirements for neurological consultation at which a full neurological examination is to be performed by a neurologist are detailed in [Section 7.3.8](#).
- ^d Subject Daily / Weekly Assessments (IRT) - Compliance with IRT assessments is to be reviewed at each study visit, including telephone visits.
- ^e Rescue medication use must be discontinued 24 hours prior to any on site study visit up to and including Week 32 (including during the Early Termination Follow-Up period). Subjects should bring back rescue medication bottles at each study visit for assessment of compliance.
- ^f If needed, following completion of the visit at which final efficacy assessments are collected (Week 32, 16 weeks after the last dose of investigational product administered), standard of care treatment (as described in [Section 6.3.2](#).) may be initiated, and usage recorded on the concomitant medication CRF.
- ^g Serum pregnancy tests are obtained at Screening, Weeks 24 and 32 or Early Termination Visits 1 and 2 for subjects who discontinue (Refer to [Section 6.4](#).). A urine pregnancy test will be obtained and confirmed as negative prior to dosing at Baseline before initial dosing, and at Weeks 8 and 16. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.
- ^h Biomarker samples should be collected at approximately the same time of the day at all scheduled time points and as much as possible following a fasting period of at least 8 hours. Fasting status should be recorded on the eCRF. Urine collected for biomarkers should be the second or later void of the day.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Tanezumab (PF-04383119, formerly RN624) is an anti-nerve growth factor monoclonal antibody under development for the relief of signs and symptoms of osteoarthritis (OA). Full details can be found in the Investigator's Brochure.¹

1.2. Background and Rationale

1.2.1. Role of Nerve Growth Factor in the Modulation of Pain

During mammalian development, nerve growth factor (NGF) is required for the survival and growth of several populations of neurons. In adults, the effect of NGF signaling shifts from the regulation of neuronal survival to the regulation of neuronal phenotype and function. The role of NGF in the adult mammal appears to principally be as a modulator of nociceptive neuronal activity and modulation of the pain response.^{3,4} Many non-clinical studies employing a variety of antibodies to NGF or IgG fusion proteins coupled to tropomyosin receptor kinase A (trkA; one of the primary receptors for NGF) have demonstrated that blocking NGF bioactivity normalizes pain sensitivity.^{4,5} Together these observations suggest that NGF may play a role in pain secondary to inflammation or injury.

1.2.2. Description of Investigational Product

Tanezumab is a humanized immunoglobulin G Type 2 (IgG₂) monoclonal antibody, derived from a murine precursor with a mutation in the Fc portion of the antibody to decrease its ability to activate complement or to support antibody dependent cell-mediated cytotoxicity.^{6,7} Tanezumab is highly potent in sequestering NGF and preventing interaction with the trkA or p75 receptors.

1.2.3. Overview of Clinical Studies

A total of 32 clinical studies involving over 11,000 subjects have been conducted with tanezumab as of September 2014. Most of these studies were conducted in subjects with osteoarthritis of the knee or hip. A total of 17 clinical studies (4 Phase 2 studies and 13 Phase 3 studies [10 controlled]) were initiated to provide evidence of efficacy and safety of tanezumab with intravenous (IV) or subcutaneous (SC) administration for the relief of the signs and symptoms of osteoarthritis alone or in combination with non-steroidal anti-inflammatory drugs (NSAIDs). In addition to the osteoarthritis studies, 11 Phase 1/2 studies were conducted to examine the efficacy and safety of tanezumab in other musculoskeletal, neuropathic, and visceral chronic pain conditions, and 2 Phase 2 studies were conducted in cancer subjects with metastatic bone pain. In these studies, tanezumab was administered by IV or SC administration every 8 weeks at fixed doses ranging from 1 mg to 20 mg or equivalent body-weight adjusted doses up to 100 mg.

Robust efficacy was demonstrated in osteoarthritis and chronic low back pain studies. Efficacy and safety results observed in non-cancer pain populations are described in the tanezumab Investigator's Brochure¹ and in external publications of individual studies.^{8,9,10,11,12,15}

1.2.3.1. Overview of Efficacy in Osteoarthritis Clinical Studies

Across the 3 co-primary measures of efficacy in four completed Phase 3 studies of tanezumab monotherapy (IV administration), doses of 2.5 mg, 5 mg, and 10 mg provided significant improvement over placebo treatment. All of the tanezumab doses tested were consistently efficacious. In Studies A4091011⁸ and A4091014⁹, the degree of mean improvement across the three efficacy domains was similar and generally dose ordered with tanezumab 10 mg providing the greatest mean response in each of the 6 comparisons to placebo treatment although only small differences in the magnitude of response were evident among the three doses of tanezumab. In Studies A4091015¹⁰ and A4091018¹⁰, tanezumab 5 mg provided modestly greater mean improvement over tanezumab 10 mg across most of the co-primary endpoints.

Further details on the efficacy of tanezumab on osteoarthritis can be found in the Investigator's Brochure (IB).¹

1.2.3.2. Overview of Safety in Clinical Studies

Based on data from all subject populations who have received tanezumab in completed clinical studies to date, the adverse drug reactions listed [Table 3](#) are considered to be expected in subjects who are treated with tanezumab.

Table 3. ADVERSE DRUG REACTIONS IN ALL SUBJECTS RECEIVING TANEZUMAB

| System Organ Class | Adverse Drug Reactions | Frequency ² |
|--|---|------------------------|
| Nervous system disorders | Burning sensation Carpal tunnel syndrome Hyperesthesia Hypoesthesia Paresthesia | Common |
| | Allodynia Neuropathy peripheral | Uncommon |
| Musculoskeletal and connective tissue disorders | Rapidly Progressive Osteoarthritis (in patients with underlying osteoarthritis) ¹ | Uncommon |
| | Arthralgia Joint swelling Myalgia Pain in extremity | Common |
| General disorders and administration site conditions | Oedema peripheral | Common |

¹ Rapidly Progressive Osteoarthritis may occur in subjects with underlying osteoarthritis. The frequency is estimated from adjudicated events of rapidly progressive osteoarthritis in historic clinical studies of tanezumab, which did not include specific risk minimization measures for this adverse reaction.

² Common (≥1% and <10%); Uncommon (≥0.1% and <1%).

A total of 7491 subjects were treated in 9 controlled Phase 3 osteoarthritis studies. The majority of these subjects were treated in studies using IV administration of tanezumab; however, approximately 900 subjects were treated in 2 studies in subjects with osteoarthritis using SC administration. The adverse event profile of SC administration of tanezumab is

comparable to the IV route based on the results of study A4091027¹³ which compared SC versus IV administration in subjects with osteoarthritis. The incidence of adverse events, withdrawals due to adverse events, and serious adverse events in subjects treated with tanezumab monotherapy (5-10 mg) was similar to subjects receiving active comparator treatment and increased over placebo-treated subjects. In the tanezumab 2.5 mg monotherapy treatment group, the incidence of adverse events was similar to active comparator while the incidence of withdrawals due to adverse events, and serious adverse events was similar to that of the placebo treatment group. Across the tanezumab monotherapy doses, the rates of adverse events, withdrawals due to adverse events, and serious adverse events, were similar with tanezumab 5 mg and 10 mg, and elevated in comparison to tanezumab 2.5 mg. Tanezumab/NSAID combination therapy was associated with higher overall adverse event rates. The relationship of incidence to the dose of tanezumab administered was similar to that seen with tanezumab monotherapy.

Based on data from the Phase 3 osteoarthritis studies and results of an independent adjudication of investigator-reported adverse events of osteonecrosis and total joint replacements, the risk of rapidly progressive osteoarthritis with tanezumab treatment was greater than with placebo or active comparator treatment.

Among the most frequently reported adverse events in the controlled Phase 3 osteoarthritis studies, the incidence of peripheral edema, upper respiratory tract infection, fall, arthralgia, back pain, joint swelling, pain in extremity, hypoesthesia, and paresthesia tended to be higher in subjects receiving tanezumab monotherapy than subjects receiving either placebo or active comparator treatment. The incidence of peripheral edema, arthralgia, joint swelling, pain in extremity, and paresthesia increased with increasing doses of tanezumab monotherapy. The adverse events with increased incidence observed with active comparator over tanezumab monotherapy included the following: constipation, nausea, urinary tract infection, nasopharyngitis, osteoarthritis, and hypertension.

The most common adverse events reported in the non-controlled, long-term Phase 3 osteoarthritis studies were similar to those seen in the controlled Phase 3 osteoarthritis studies with the exception of the inclusion of musculoskeletal pain and exclusion of hypertension and nasopharyngitis and all gastrointestinal-related adverse events. Dose-related increases in the incidence of peripheral edema, joint swelling, osteoarthritis and paresthesia were observed.

1.2.3.2.1. Sympathetic Nervous System

In completed Phase 3 osteoarthritis studies, the incidence and discontinuation rates due to adverse events consistent with decreased sympathetic function associated with tanezumab monotherapy (combined doses of 2.5 to 10 mg) were less than or equal to rates with placebo or active comparator. No evidence of dose related elevations in the frequency of adverse events suggestive of decreased sympathetic nervous system function were observed at doses of 2.5 to 10 mg in subjects with osteoarthritis. Tanezumab 20 mg in chronic low back pain had marginally higher event rates compared to placebo and active comparator treatment groups.

Based on completed osteoarthritis studies where orthostatic blood pressure, heart rate deep breathing, or autonomic symptoms captured with the Neuropathy Symptom Change (NSC) questionnaire were specifically assessed, the data are not suggestive of an adverse effect of tanezumab on autonomic function.

Although evidence of clinically important effects on the sympathetic nervous system have not been identified in previously completed tanezumab studies, per agreement with the Food and Drug Administration (FDA), this and other clinical studies of tanezumab will incorporate additional safety measures to monitor for and manage subjects who may develop evidence of clinically important sympathetic nervous system dysfunction.

1.2.3.2.2. Joint Safety

A comprehensive investigation and analyses related to joint-safety has been conducted, based on tanezumab monotherapy exposure in over 6400 subjects and tanezumab/NSAID combination therapy in 3400 subjects. There were over 5000 subjects who received tanezumab treatment alone or in combination with NSAIDs for 6 months or longer. The program was sufficient to define and characterize the adverse event of concern – rapidly progressive osteoarthritis – and evaluate the risk of rapidly progressive osteoarthritis in the context of the overall benefit-risk profile of tanezumab compared to standard of care. The results and conclusions regarding tanezumab and the other anti-NGF therapies are provided in detail elsewhere.¹

After careful investigation, no evidence was found to substantiate that tanezumab is associated with an increased risk of osteonecrosis, a disease process quite distinct from osteoarthritis. A risk of rapidly progressive osteoarthritis was identified. The risk of rapidly progressive osteoarthritis with tanezumab monotherapy was well below that observed with tanezumab/NSAID combination therapy but greater than with placebo or active comparator treatment. A majority of subjects identified with rapidly progressive osteoarthritis had advanced osteoarthritis of the affected joint prior to treatment. The event rate of all-cause joint replacements in subjects with osteoarthritis was comparable among placebo, active comparator, and tanezumab monotherapy treatment groups. Further details can be found in the IB.¹

Risk mitigation measures have been developed as an outgrowth of the joint-related safety analyses to reduce the risk of rapidly progressive osteoarthritis. Using recommendations from discussions with European agencies [United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA), Germany's Paul Ehrlich Institute (PEI) and Spain's Agency on Medicinal Products and Medical Devices (AEMPS)] as well as the 2012 FDA Arthritis Advisory Committee and interactions with FDA, risk mitigation measures were developed. These risk mitigation measures have been included in this study and are outlined as follows:

Risk Minimization: (1) exclude chronic concomitant NSAID use, (2) exclude tanezumab doses that have been explored and do not demonstrate benefit over lower doses in the condition under study, (3) exclude subjects with evidence of rapidly progressive osteoarthritis or risk factors for such from participating in clinical studies, (4) discontinue

treatment with investigational product in subjects who fail to achieve adequate pain relief and (5) exclude subjects who are not suitable candidates for total joint replacement from study participation.

Risk Identification and Management: (1) evaluation and follow-up for severe persistent joint pain, (2) extended post-treatment follow-up, (3) a program-level Central Radiograph Reader and subject-level stopping criteria, (4) an Adjudication Committee, and (5) a Data Monitoring Committee and protocol-level stopping rules.

Risk Characterization: (1) Comprehensive evaluation of osteoarthritis medical history prior to study entry, (2) scheduled radiographic assessments during the studies, (3) surgical and post-operative total joint replacement outcomes, and (4) biomarker determinations.

1.2.3.3. Subcutaneous Administration of Tanezumab in Clinical Studies

The formulation of tanezumab that has been administered by SC injection is identical to what has been administered by IV infusion and is administered as a 1 mL SC injection in the thigh or abdomen. The safety and efficacy of tanezumab when administered by SC injection has been evaluated in OA subjects primarily in two studies, A4091027¹³ and A4091043,¹⁴ and in subjects with chronic low back pain in one study (A4091039¹⁵). A total of 1905 subjects were treated in these studies. The observed efficacy and safety profile of tanezumab administered SC was similar to IV administration.

1.2.4. Dose Selection Rationale

Intravenous and SC administration of tanezumab at doses of 2.5 mg, 5 mg and 10 mg was shown to reduce pain and improve function in a dose-related manner in Phase 3 studies of osteoarthritis. As one of the risk mitigation features identified through analysis of orthopedic safety and efficacy data, no further study of the tanezumab 10 mg dose will be conducted in subjects with osteoarthritis as this dose did not provide sufficient additional efficacy benefit over the 5 mg dose. The 5 mg dose is expected to provide added efficacy benefit over the 2.5 mg dose. Based upon prior studies, this additional efficacy benefit is likely to be most evident in subjects considered to have severe symptomatic osteoarthritis as defined above in [Section 1.2.3.1](#). The current study will therefore investigate the safety and efficacy of fixed-dose levels of tanezumab 2.5 mg and 5 mg administered up to 3 times at 8-week intervals relative to placebo.

1.2.5. Rationale for Placebo Treatment

The use of a placebo comparator is the gold-standard for assessing efficacy in short-term pain studies. Utilization of placebo as a comparator allows a smaller sample size and thus demonstrates the study objectives of efficacy more efficiently than a study using an active comparator. In addition, the use of a placebo arm is most important when the trial endpoints are subjective measures such as those used in this study, because of the often great variation in the way individuals perceive subject-reported outcomes. This was reported to be particularly relevant for studies involving pain relief, depression, and asthma.¹⁶ In this study SC placebo is used to blind investigators and subjects as to whether or not SC tanezumab has been administered. Although no analgesic efficacy is expected from placebo treatment, some

placebo-treated subjects may experience a beneficial effect on well-being. Rescue medication (acetaminophen/paracetamol) will be allowed to all subjects throughout the study (refer to [Section 5.8](#)).

1.2.6. Subject Population Selection Rationale

The population selected for this study is subjects with moderate to severe osteoarthritis pain of the hip or knee based on American College of Rheumatology criteria with X-ray confirmation (a Kellgren-Lawrence x-ray grade of ≥ 2) who have had inadequate pain relief with previous conventional pharmacological treatment options for osteoarthritis, or who are unable to take these medications due to a contraindication or the inability to tolerate them and who are seeking effective treatment options other than or prior to joint replacement. The rationale for the choice of this population is to optimize the potential benefit:risk relationship for subjects entering the study by selecting subjects who have pain that is more severe or treatment resistant and who have limited treatment options remaining.

Complete information for this compound may be found in the Single Reference Safety Document, which for this study is the Investigator's Brochure.¹

1.2.7. Benefit-Risk Assessment.

The determination of the benefit-risk assessment must take into account the efficacy and safety of tanezumab, and the population to be studied in this protocol.

Tanezumab has been studied for use in moderate to severe chronic pain conditions including osteoarthritis. Data from the available Phase 2 and 3 studies has shown that tanezumab treatment provides significant improvements in pain, physical function and global assessment in osteoarthritis compared with placebo, NSAID and opiate treatment.

Concerning safety, relative to placebo, tanezumab monotherapy and active comparator treatment groups, tanezumab/NSAID treatment groups were associated with the highest overall adverse event rate and rate of discontinuations due to adverse events in Phase 3 osteoarthritis studies. The incidence of adverse events and discontinuations due to adverse events in Phase 3 studies in patients with osteoarthritis increased with increasing tanezumab dose and with the combination of tanezumab and NSAID. (See Investigator's Brochure [Section 6.2.1](#).)

The rate of all-cause total joint replacements (patients who underwent total joint replacement + patients with reported osteonecrosis regardless of whether they underwent total joint replacement or not) in patients with osteoarthritis was comparable between placebo, active comparator and tanezumab monotherapy treatment groups. The rate of all-cause total joint replacements did not increase with increasing tanezumab monotherapy dose. (See Investigator's Brochure [Section 6.2.10](#) and [Section 1.2.3.2.2](#) of Protocol A4091057). The rate of rapidly progressive osteoarthritis increased with increasing tanezumab dose and was elevated above the rate observed in placebo and active comparator treatment groups. The combination of tanezumab + NSAID treatment increased the rate of rapidly progressive osteoarthritis and all-cause total joint replacement by >2 to 3-fold above other treatment

groups. Because of those findings, risk mitigation measures have been incorporated into the protocol (see [Section 1.2.3.2.2](#)).

Adverse events of abnormal peripheral sensation with tanezumab treatment have been observed in all patient populations studied to date. The adverse events are dose-related, generally resolve and are of mild-to-moderate intensity at the doses planned for future studies. (See Investigator's Brochure [Section 6.2.11](#)).

Based upon quantitative sensory testing, intraepidermal nerve fiber density, nerve conduction velocity testing and heart rate deep breathing assessments conducted to-date, administration of tanezumab does not have a clinically meaningful effect on sensory or autonomic nerve function based on data in healthy volunteers or patients with osteoarthritis or painful diabetic peripheral neuropathy (See Investigator's Brochure [Section 6.2.11.4](#)).

Clinically meaningful changes in vital signs, laboratory values, or electrocardiograms (ECG) (including QTc) have not been observed to-date (See Investigator's Brochure [Section 6.2](#)).

In summary, tanezumab treatment has been shown to provide significant improvements in pain, physical function and global assessment in osteoarthritis compared to placebo, NSAID and opiate treatment. The benefit to subjects participating in the study will be the potential for improvement in osteoarthritis pain that has not been adequately relieved by previous treatment regimens.

Based on the overall assessment of risk and benefit, the data support further clinical investigation of tanezumab with the additional benefit-risk optimization and surveillance measures employed as outlined in the protocol.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

PRIMARY OBJECTIVE

- Demonstrate superior efficacy of tanezumab 5 mg and 2.5 mg administered subcutaneously (SC) every 8 weeks versus placebo at Week 24.

SECONDARY OBJECTIVE

- Evaluate the safety of tanezumab 2.5 mg SC and 5 mg SC.

2.2. Endpoints

2.2.1. Co-primary Efficacy Endpoints:

- Change from Baseline to Week 24 in the WOMAC Pain subscale.
- Change from Baseline to Week 24 in the WOMAC Physical Function subscale.
- Change from Baseline to Week 24 in the Patient's Global Assessment of Osteoarthritis.

2.2.2. Secondary Endpoints

2.2.2.1. Efficacy Measures

- WOMAC Pain subscale change from Baseline to Weeks 2, 4, 8, 12, 16, and 32.
- WOMAC Physical Function subscale change from Baseline to Weeks 2, 4, 8, 12, 16, and 32.
- Patient's Global Assessment of Osteoarthritis (5 point Likert scale) change from Baseline to Weeks 2, 4, 8, 12, 16, and 32.
- OMERACT-OARSI responder index at Weeks 2, 4, 8, 12, 16, 24, and 32.
- Cumulative distribution of percent change from Baseline in the WOMAC Pain subscale score to Week 16 and 24 (endpoint for summary only).
- Treatment Response: Reduction in the WOMAC Pain subscale of $\geq 30\%$, $\geq 50\%$, $\geq 70\%$ and $\geq 90\%$, at Weeks 2, 4, 8, 12, 16, 24, and 32.
- Treatment Response: Reduction in the WOMAC Physical Function subscale of $\geq 30\%$, $\geq 50\%$, $\geq 70\%$ and $\geq 90\%$ at Weeks 2, 4, 8, 12, 16, 24, and 32.
- Cumulative distribution of percent change from Baseline in the WOMAC Physical Function subscale score to Week 16 and 24 (endpoint for summary only).
- Treatment Response: Improvement of ≥ 2 points in Patient's Global Assessment of Osteoarthritis at Weeks 2, 4, 8, 12, 16, 24, and 32.
- Average pain score in the index knee or hip change from Baseline to Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 28 and 32.
- WOMAC Stiffness subscale change from Baseline to Weeks 2, 4, 8, 12, 16, 24 and 32.
- WOMAC Average score change from Baseline to Weeks 2, 4, 8, 12, 16, 24, and 32.
- WOMAC Pain Subscale Item: Pain When Walking on a Flat Surface, change from Baseline to Weeks 2, 4, 8, 12, 16, 24, and 32.
- WOMAC Pain Subscale Item: Pain When Going Up or Downstairs, change from Baseline to Weeks 2, 4, 8, 12, 16, 24, and 32.
- Work Productivity and Activity Impairment Questionnaire for Osteoarthritis (WPAI:OA) impairment scores change from Baseline to Weeks 8, 16 and 24.
- EQ-5D-5L Health State Utility and Five Items (Mobility; Self-Care; Usual Activities; Pain/Discomfort; Anxiety/Depression) change from Baseline to Weeks 8, 16 and 24.

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- Patient Reported Treatment Impact Assessment-Modified (mPRTI) at Weeks 16 and 24.
- Health Care Resource Utilization at Baseline, and Weeks 32 and 48.
- Incidence and time to discontinuation due to Lack of Efficacy.
- Usage of rescue medication (incidence and number of days of use) during Weeks 2, 4, 8, 12, 16, 24, and 32.
- Usage of rescue medication (amount taken) during Weeks 2, 4, 8, 12, 16 and 24.

2.2.2.2. Safety Measures

- Adverse Events.
- Standard safety assessments (safety laboratory testing [chemistry, hematology], sitting vital signs, electrocardiogram (ECG; 12-lead).
- Joint Safety Adjudication outcomes.
- Total joint replacements.
- Orthostatic (supine / standing) blood pressure assessments.
- Survey of Autonomic Symptom scores.
- Neurologic exam (Neuropathy Impairment Score [NIS]).
- Anti-tanezumab antibody assessments.
- Physical examinations.

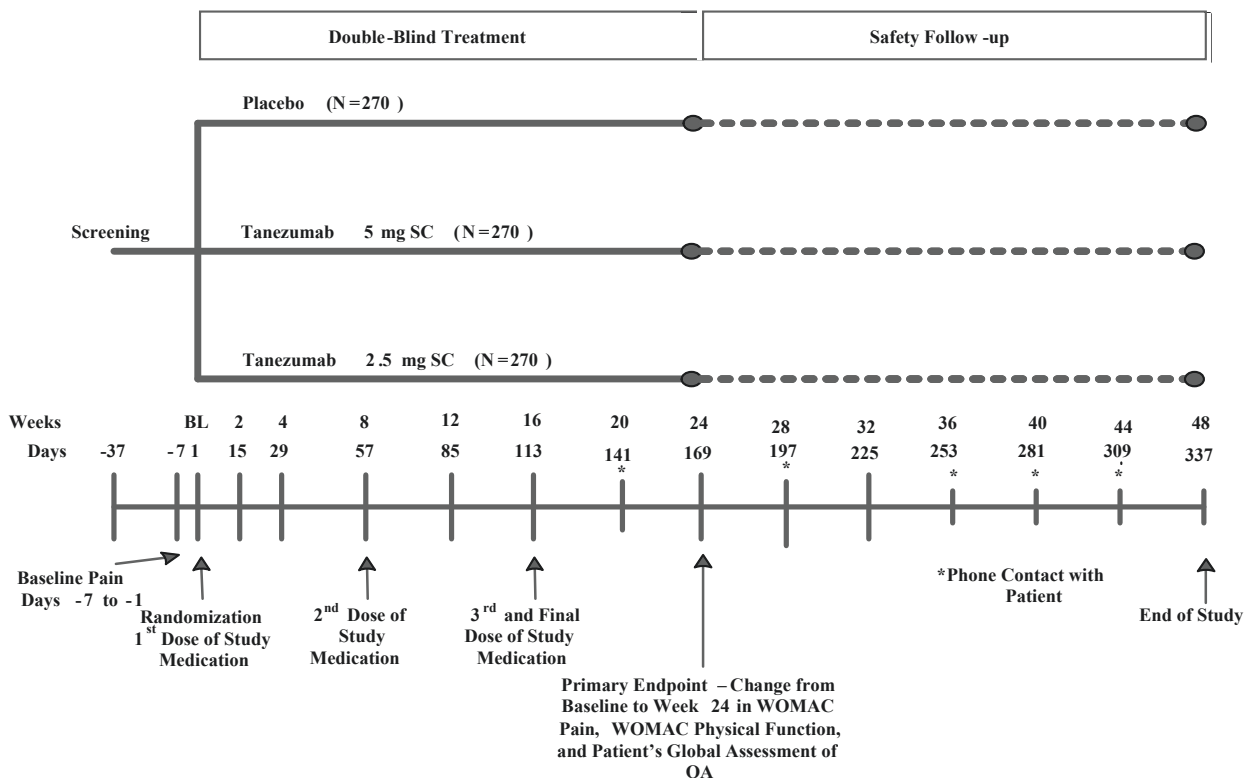
2.2.3. Tertiary Endpoints

2.2.3.1. Pharmacokinetic and Pharmacodynamic

- Plasma tanezumab concentrations.
- Serum NGF assessment.
- Serum and urine osteoarthritis biomarker concentrations.

3. STUDY DESIGN

Figure 1. Study Schematic



This is a randomized, double-blind, placebo-controlled, parallel-group multicenter Phase 3 study of the efficacy and safety of tanezumab when administered by SC injection for 24 weeks compared to placebo in subjects with osteoarthritis of the knee or hip. A total of approximately 810 subjects will be randomized to 1 of 3 treatment groups in a 1:1:1 ratio (ie, 270/group). The randomization will be stratified by index joint (hip or knee), and most severe Kellgren-Lawrence grade (of any knee or hip joint) at study entry (grade 2, 3 or 4). Subjects will receive up to three SC doses of one of the following treatments at an 8-week interval between each injection:

1. tanezumab 2.5 mg;
2. tanezumab 5 mg;
3. Placebo to match tanezumab.

The study is designed with a total (post-randomization) duration of 48 weeks and will consist of three periods: Screening (up to 37 days), Double-blind Treatment (24 weeks) and Safety Follow-up (24 weeks). The Screening Period (beginning up to 37 days prior to Randomization) includes a Washout Period (lasting a minimum of 2 days for all prohibited pain medications), if required, and an Initial Pain Assessment Period (the 7 days prior to Randomization/Baseline).

Week 24 is the landmark analysis in this study.

Subjects who complete the Week 24 visit will be considered to have completed the Double-blind Treatment period and will enter the 24-week Safety Follow-up period. Subjects who have completed the Double-blind Treatment period and have entered the 24-week Safety Follow-up period and complete the Week 48 visit will be considered to have completed the study. Subjects who discontinue study treatment prior to completing the Week 24 visit will not be considered to have completed the Double-blind Treatment period. Subjects who do not complete the Double-blind Treatment period but who enter and complete the 24-week Early-termination follow-up period will be considered to have completed the study while those subjects who do not complete the 24-week Early-termination follow-up period will not be considered to have completed the study.

For subjects who withdraw from the study, see [Section 6.4](#). Every effort should be made to have the subject agree to complete the entire 24-week Early Termination Safety Follow-up.

The procedure for subjects in Japan who have not had a trial of acetaminophen is described in [Section 6.1.1](#).

Details relevant to the study design can be found in [Sections 6 and 7](#) and the Schedule of Activities ([Tables 1 and 2](#)).

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study.

1. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative) has been informed of all pertinent aspects of the study.
2. Male or female ≥ 18 years of age.
3. A diagnosis of osteoarthritis of the hip or knee in the index joint based on American College of Rheumatology criteria with x-ray confirmation (a Kellgren-Lawrence¹⁷ x-ray grade of ≥ 2 as diagnosed by the Central Reader; [Appendix 1](#)).
4. Documented history indicating that:

- acetaminophen therapy has not provided sufficient pain relief;
- oral NSAID therapy has not provided adequate pain relief or subject is unable to take NSAIDs due to contraindication or inability to tolerate.

AND at least 1 of the following criteria:

- Documented history indicating that tramadol treatment has not provided adequate pain relief or subject is unable to take tramadol due to contraindication or inability to tolerate,
 - Documented history indicating that opioid treatment has not provided adequate pain relief or subject is unwilling to take opioids, or unable to take opioids due to contraindication or inability to tolerate.
5. WOMAC Pain subscale Numerical Rating Scale (NRS) ≥ 5 in the index joint at Screening.
6. Subjects must be willing to discontinue all pain medications for osteoarthritis except rescue medication (acetaminophen) and not use prohibited pain medications throughout the duration of the study except as permitted per protocol.
7. Female subjects of childbearing potential and at risk for pregnancy must agree to use 2 highly effective or acceptable methods of contraception throughout the study and for 112 days (16 weeks) after the last dose of assigned subcutaneous investigational product.

NOTE: In Japan, only female subjects who are not of childbearing potential will be eligible for this study.

NOTE: In Sweden, female subjects of childbearing potential and at risk for pregnancy must agree to use at least one highly effective method of contraception throughout the study and for 112 days (16 weeks) after the last dose of assigned subcutaneous study medication.

8. Female subjects who are not of childbearing potential meet at least one of the following criteria:
- Have undergone a documented hysterectomy and/or bilateral oophorectomy;
 - Have medically confirmed ovarian failure; or
 - Achieved post-menopausal status defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and have a serum follicle stimulating hormone (FSH) level confirming the post-menopausal state.

9. Subjects who are willing and able to comply with lifestyle guidelines, scheduled visits, treatment plan, laboratory tests, and other study procedures through the End of Study visit.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, or subjects who are Pfizer employees directly involved in the conduct of the trial.
2. Body Mass Index (BMI) of $>39 \text{ kg/m}^2$.
3. History of other disease that may involve the index joint including inflammatory joint disease such as rheumatoid arthritis, seronegative spondyloarthropathy (eg, ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease related arthropathy), crystalline disease (eg, gout or pseudogout), endocrinopathies, metabolic joint diseases, lupus erythematosus, joint infections, Paget's disease, or tumors.
4. Radiographic evidence of any of the following conditions in any screening radiograph as determined by the central radiology reviewer and as defined in the tanezumab program imaging atlas: excessive malalignment of the knee, severe chondrocalcinosis; other arthropathies (eg, rheumatoid arthritis), systemic metabolic bone disease (eg, pseudogout, Paget's disease, metastatic calcifications), large cystic lesions, primary or metastatic tumor lesions, stress or traumatic fracture.
5. Radiographic evidence of any of the following conditions as determined by the central radiology reviewer and as defined in the tanezumab program imaging atlas at Screening:
1) rapidly progressive osteoarthritis, 2) atrophic or hypotrophic osteoarthritis, 3) subchondral insufficiency fractures, 4) spontaneous osteonecrosis of the knee (SPONK), 5) osteonecrosis, or 6) pathologic fracture.
6. A history of osteonecrosis or osteoporotic fracture (ie, a subject with a history of osteoporosis and a minimally traumatic or atraumatic fracture).
7. History of significant trauma or surgery to a knee, hip or shoulder within the previous year.
8. Planned surgical procedure during the duration of the study.
9. Largely or wholly incapacitated, (eg, subject bedridden or confined to a wheelchair, permitting little or no self-care).
10. Fibromyalgia, regional pain caused by lumbar or cervical compression with radiculopathy or other moderate to severe pain that may confound assessments or self-

evaluation of the pain associated with osteoarthritis. Subjects with a present (current) history of sciatica are not eligible for participation. Subjects with a past history of sciatica who have been asymptomatic for at least one year and who have no evidence of radiculopathy or sciatic neuropathy on thorough neurologic examination are eligible for participation.

11. Subjects with a past history of carpal tunnel syndrome (CTS) with signs or symptoms of CTS in the one year prior to Screening.
12. Subjects considered unfit for surgery, defined as Grade >3 on the American Society of Anesthesiologists (ASA) physical classification system for surgery (see [Appendix 2](#)), or subjects who would not be willing to undergo joint replacement surgery if required.
13. History of intolerance or hypersensitivity to acetaminophen (paracetamol) or any of its excipients or existence of a medical condition or use of concomitant medication for which the use of acetaminophen is contraindicated (refer to product labeling).
14. Use of prohibited medications without the appropriate washout period (if applicable) prior to Screening or Initial Pain Assessment Period (refer to [Section 5.7.1](#)).
15. Oral or intramuscular corticosteroids within 30 days prior to the Initial Pain Assessment Period.
16. Intra-articular corticosteroid injection in the index joint within 12 weeks, or to any other joint within 30 days prior to the Initial Pain Assessment Period.
17. Intra-articular hyaluronic acid injection in the index joint within 30 days (or within 18 weeks for long-acting formulations such as Synvisc) prior to the Initial Pain Assessment Period.
18. History of cancer within 5 years prior to Screening, except for cutaneous basal cell or squamous cell cancer resolved by excision.
19. Signs and symptoms of clinically significant cardiac disease including but not limited to:
 - Ischemic cardiac disease (eg, unstable angina, myocardial infarction) in the 6 months prior to Screening;
 - Surgery or stent placement for coronary artery disease in the 6 months prior to Screening;
 - New York Heart Association (NYHA) Class III or IV congestive heart failure or known left ventricular dysfunction with ejection fraction $\leq 35\%$, cardiomyopathy, myocarditis in the 6 months prior to Screening;
 - Resting tachycardia (heart rate ≥ 120) or resting bradycardia (heart rate ≤ 45) on ECG at Screening;

- QTcF interval >500 msec in the absence of confounding factors like bundle branch block or paced rhythm at Screening;
- Any other cardiovascular illness that in the opinion of the investigator would render a subject unsuitable to participate in the study.
- Subjects with a history of heart block.

Patients with a history of heart block now controlled by a functioning cardiac pacemaker and/or transient episodes of asymptomatic tachy- or bradyarrhythmia are eligible.

20. Diagnosis of a transient ischemic attack in the 6 months prior to Screening, diagnosis of stroke with residual deficits (eg, aphasia, substantial motor or sensory deficits), that would preclude completion of required study activities.

21. History, diagnosis, or signs and symptoms of clinically significant neurological disease, including but not limited to:

- Alzheimer's disease or other types of dementia;
- Clinically significant head trauma within the past year;
- Peripheral or autonomic neuropathy;
- Multiple sclerosis
- Epilepsy or seizure disorder with history of seizure within the last 2 years;
- Myopathy.

22. History, diagnosis, signs or symptoms of any clinically significant psychiatric disorder, including but not limited to:

- Psychotic disorders;
- Somatoform disorders;
- Bipolar disorders;
- Hospital admission for depression or suicide attempt within 5 years of Screening, or active severe major depression at Screening (determined from medical history: if needed, severity of depression may be assessed using the Patient Health Questionnaire [PHQ-9]).¹⁸ A score of ≥ 15 on questions 1-9 of the PHQ-9 corresponds to severe depression. See [Appendix 9](#));

- Any other psychiatric illness that in the opinion of the investigator would render a subject unsuitable to participate in the study.
23. History of known alcohol, analgesic or drug abuse within 2 years of Screening.
24. Previous exposure to exogenous NGF or to an anti-NGF antibody.
25. History of allergic or anaphylactic reaction to a therapeutic or diagnostic monoclonal antibody or IgG-fusion protein.
26. Resting, sitting blood pressure (BP) ≥ 160 mm Hg in systolic pressure or ≥ 100 mm Hg in diastolic pressure at Screening. If a subject is found to have untreated significant hypertension at Screening and antihypertensive treatment is initiated, assessment for study eligibility should be deferred until BP and antihypertensive medication have been stable for at least one month. For subjects with previously diagnosed hypertension, antihypertensive medications must be stable for at least 1 month prior to Screening.
27. Subjects who have evidence of orthostatic hypotension based upon replicate orthostatic blood pressure measurements (refer to [Section 7.3.4.1](#)). If orthostatic blood pressure change is not able to be determined (eg, unable to establish a stable supine systolic and diastolic blood pressure) then subject is not eligible for the study.
28. Subjects with a total impact score of >7 on the Survey of Autonomic Symptoms (SAS, see [Appendix 11](#)).
29. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3.0 times the upper limit of normal, or creatinine exceeding 1.7 mg/dL (150 μ mol/L) in men or 1.5 mg/dL (133 μ mol/L) in women, or hemoglobin A1c $\geq 10\%$ at Screening. Repeat confirmatory tests may be performed.
30. Presence of drugs of abuse (including prescription medications without a valid prescription), or illegal drugs in the urine toxicology screen obtained at Screening.
31. Positive Hepatitis B, Hepatitis C, or Human Immunodeficiency Virus (HIV) tests at Screening indicative of current infection.
32. Participation in other studies involving investigational drug(s) within 30 days (or 90 days for biologics) prior to study entry and/or during study participation.
33. Pregnant female subjects; breastfeeding female subjects; female subjects of childbearing potential who are unwilling or unable to use two (2) highly effective or acceptable methods of contraception as outlined in this protocol for the duration of the study and for 112 days (16 weeks) after last dose of investigational product.

NOTE: In Sweden, pregnant female subjects; breastfeeding female subjects; female subjects of childbearing potential who are unwilling or unable to use one (1) highly

effective method of contraception as outlined in this protocol for the duration of the study and for 112 days (16 weeks) after last dose of investigational product.

34. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

4.3. Randomization Criteria

In addition to meeting all inclusion and exclusion criteria requirements listed above, there are requirements for the following to be met before randomization can be called into the interactive response technology (IRT) system at the Baseline visit:

1. Subject must have completed appropriate washout of analgesics.
2. Subject must have made at least 3 pain diary entries in the 7 days prior to the Baseline (Day 1) visit.
3. Subject must have abstained from taking rescue medication (acetaminophen/paracetamol) within the 24 hours that precede dosing.
4. WOMAC Pain subscale NRS ≥ 5 in the index knee or index hip at Baseline.
5. WOMAC Physical Function subscale NRS ≥ 5 in the index knee or index hip at Baseline
6. Patient's Global Assessment of Osteoarthritis must be "fair", "poor," or "very poor" at Baseline.
7. Review of the ECG and laboratory results and confirmation that there are no clinically significant or exclusionary findings.
8. Subject must have had required Baseline x-rays.
9. Radiographic eligibility must have been confirmed by the Central Reader.

4.4. Life Style Guidelines

Subjects should maintain their normal daily routine, including stable doses of permitted medications and exercise program. Subjects may continue with non-pharmacologic activities (eg, massage, physical therapy) during the trial. Subjects should be cautioned against initiating or altering strenuous exercise regimens during the study as this may influence efficacy and laboratory results. Subjects will be advised to avoid elective surgery (eg, oral surgery) during the course of the study if possible; the study clinician should be contacted for discussion prior to any surgery whenever possible. Subjects who undergo joint replacement or arthroplasty will be discontinued from investigational product and followed as described in [Section 6.4.2](#).

Refer to [Section 5.7.2](#) and [Section 5.7.1](#), and [Appendix 3](#) for guidance on permitted and prohibited medications.

All female subjects who, are of child-bearing potential and are sexually active and at risk for pregnancy, must agree to use two (2) methods of contraception (from the options listed below) consistently and correctly for the duration of the active treatment period and for 112 days (16 weeks) after the last dose of SC investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected the appropriate methods of contraception for the individual subject from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of at least two of the selected methods of contraception. The investigator or his or her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation in the subject's chart. In addition, the investigator or his/or her designee will instruct the subject to call immediately if the selected contraception methods are discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include, with the exception of number 3 which is an acceptable birth control method:

1. Established use of oral, inserted, injected, implanted, or transdermal hormonal methods of contraception is allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness, with the exception of oral low-dose progestogens for which inhibition of ovulation is not the primary mode of action, and therefore such a method is not considered a highly effective contraceptive method.
2. Correctly placed copper containing intrauterine device (IUD).
3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.
4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.
5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

NOTE: For Sweden, please refer to [Appendix 14](#) for Life Style Guidelines concerning contraception for subjects from clinical sites in this country.

4.5. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the study manual.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study numbers, contact information for the investigational site and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact center number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

5.1. Allocation to Treatment

Subjects will be randomized at Baseline to one of the following treatment groups, all subjects will receive SC treatment during the Double-blind Treatment period of the study:

| Treatment Group | Subcutaneous Treatment (SC) |
|-----------------|--|
| 1 | Placebo for tanezumab once every 8 weeks x 3 doses |
| 2 | Tanezumab 2.5 mg once every 8 weeks x 3 doses |
| 3 | Tanezumab 5 mg once every 8 weeks x 3 doses |

Subjects will be randomly assigned in a 1:1:1 ratio to the above treatment regimens according to a computer generated randomization schedule. The randomization will be stratified by index joint (hip or knee), and most severe Kellgren-Lawrence grade (of any knee or hip joint) at study entry (grade 2, 3 or 4). This will result in a 6-group stratified randomization scheme as follows:

1. Subjects with osteoarthritis of the hip and highest Kellgren-Lawrence grade of 2;
2. Subjects with osteoarthritis of the hip and highest Kellgren-Lawrence grade of 3;
3. Subjects with osteoarthritis of the hip and highest Kellgren-Lawrence grade of 4;
4. Subjects with osteoarthritis of the knee and highest Kellgren-Lawrence grade of 2;

5. Subjects with osteoarthritis of the knee and highest Kellgren-Lawrence grade of 3;

6. Subjects with osteoarthritis of the knee and highest Kellgren-Lawrence grade of 4;

Randomization will be coordinated centrally through Interactive Response Technology (IRT). The system will provide subject identification numbers at Screening, which will subsequently be linked to the treatment assignments at Randomization. The randomization code will be securely maintained by a person(s) who is independent of the trial conduct and produces the randomization code. It is the responsibility of the Principal Investigator to ensure that the subject is eligible for participation in the study before requesting Randomization. The study site will obtain the subject's randomization number and dispensable unit identification numbers (ie, the drug supply to be administered) from the IRT. Further details will be provided in the Pharmacist Manual.

5.2. Breaking the Blind

This is a randomized, double-blind, placebo-controlled, parallel group study. The subjects, Investigators, Study Coordinators, clinical site staff, Clinical Research Associate (CRA), and staff directly involved with the study at Pfizer and its designees will be blinded to subject assignment.

Blinding should be broken only in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub-investigator consults with a member of the study team prior to breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the Case Record Form (CRF).

- The investigator or medical designee is responsible for contacting the Pfizer Clinical Support Help Desk to obtain the Principal Investigator's user account information. The account information will only be given to the investigator or medical designee.
- The investigator at each site will have the ability to break the blind on a subject in the electronic system.
- In the event the investigator is not available to perform the break blind, the Pfizer Clinician, and the Pfizer Clinical Support Help Desk, also have the ability to break the blind and can inform the Principal Investigator subsequently.

5.3. Compliance

Tanezumab and corresponding placebo dosing will be recorded on the appropriate CRF. Because tanezumab or corresponding placebo will be administered by site staff, subject compliance with SC treatment is not anticipated to be an issue.

For rescue medication (acetaminophen / paracetamol), compliance will be reviewed and reconciled at each study visit.

Protocol rules governing the use of rescue medication are described in [Section 5.8](#).

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5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

Tanezumab and placebo for tanezumab will be supplied by the Sponsor or designee.

5.4.1.1. Tanezumab

Tanezumab 2.5 mg is presented as a sterile solution for subcutaneous administration, in a glass pre-filled syringe (PFS). Each PFS contains a sufficient amount of tanezumab to provide the intended dose of drug at a concentration of 2.5 mg/mL.

Tanezumab 5 mg is presented as a sterile solution for subcutaneous administration, in a glass pre-filled syringe (PFS). Each PFS contains a sufficient amount of tanezumab to provide the intended dose of drug at a concentration of 5 mg/mL.

Each prefilled syringe is packed in an individual carton. Each prefilled syringe has a unique container number.

5.4.1.2. Placebo for Tanezumab

Placebo for tanezumab is presented as a sterile solution for subcutaneous administration, in a matching glass pre-filled syringe (PFS). Each pre-filled syringe is packaged in an individual carton. Each prefilled syringe has a unique container number.

5.4.1.3. Acetaminophen/Paracetamol (Rescue Medication)

Acetaminophen/paracetamol will be issued by the study sites in its approved marketed product dress (carton, bottle, documents). Any approved commercial product of acetaminophen/paracetamol tablet/caplet/capsule is permitted. Subjects should bring back rescue medication bottles at each study visit for assessment of compliance.

5.4.2. Preparation and Dispensing

See Dosage and Administration Instructions (DAI) for instructions on how to prepare tanezumab 2.5 mg SC, 5 mg SC and placebo SC for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

5.4.3. Administration

Tanezumab or matching placebo will be administered via SC injection by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance and at facilities which can handle allergic reactions. All subjects will receive 1 mL of investigational product administered as a SC injection. Subcutaneous injections are to be administered in the abdomen or anterior aspect of the thigh. Selection of the SC injection site for each injection will be at the discretion of the investigator taking into account subject preferences when possible. The SC injection should not be administered in areas where the skin is burned, reddened, inflamed, swollen, or scarred.

5.5. Investigational Product Storage

The Investigator or an approved representative (eg, Pharmacist) will ensure that all investigational products, including any marketed products, are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the label. See the Pharmacy Manual for storage conditions of the product.

Storage conditions stated in the single reference safety document (SRSD) (ie, Investigator's Brochure), will be superseded by the storage conditions stated in the investigational product labeling.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

5.6. Investigational Product Accountability

The Investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the drug supplies.

5.6.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If Pfizer authorizes destruction to take place at the trial site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer. Destruction must be adequately documented.

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5.7. Concomitant Treatment(s)

5.7.1. Prohibited Treatment(s)

Use of analgesics (including marijuana and duloxetine) other than acetaminophen/paracetamol is prohibited throughout Week 32 of the study beginning 48 hours prior to the start of the Initial Pain Assessment Period (the seven days prior to Randomization/Baseline) or at the period of time prior to the start of the Initial Pain Assessment Period that is ≤ 5 times the half-life of the particular analgesic used, whichever is greater. Refer to [Appendix 3: Half-Lives of Prohibited Prior and Concomitant Medications](#), for a detailed washout schedule for prohibited medications. This is not an exhaustive list and Pfizer study management should be consulted for assistance if needed, in determining whether or not specific medications are permitted. Sites must consult product labeling and conduct a taper according to the product instructions if a taper is required.

Use of prescription or over-the-counter (OTC) NSAIDs irrespective of route, eg oral, topical or rectal, (including COX-2 selective inhibitors) is also prohibited except in the following circumstances. Limited concomitant use of prescription or OTC NSAID may be allowed on an occasional basis for self-limiting conditions not related to osteoarthritis however, they may not be taken within 48 hours (or 5 half-lives, whichever is greater) of a study visit where efficacy assessments are being collected. The study monitor or Pfizer clinician should be contacted for approval prior to use whenever possible, and all doses and days of use will be recorded on the concomitant analgesic CRF. NSAID use should not exceed a total of 40 days between Day 1 (Baseline) and Week 32. Beginning at Week 32 (16-weeks after the last dose of study medication), subjects may use NSAIDs at their discretion.

Subjects will be instructed that many over-the-counter medications contain NSAIDs and to guard against overuse. Subjects will be instructed to keep a recording of NSAID usage and amount. The number of days of NSAID use will be collected weekly via IRT from Baseline (Day 1) through the Week 48 visit. Additional information regarding NSAID use such as medication names, dosage and reason for use will be collected by the site on a CRF.

NSAID usage will be monitored at 2 levels: the cumulative use from Baseline to Week 32 (a maximum of 40 days of use) and the aggregate days of use during each 8 week dosing interval (a maximum of 10 days of use).

Subjects who exceed the allowable concomitant NSAID use limit of 40 days of use during the treatment phase of the study will be discontinued from the study and entered in the Early Termination Follow-up Period. Subjects taking greater than 10 days of aggregate use of NSAIDs per 8-week dosing interval (any dosage level of NSAIDs) should be interviewed by study site personnel to determine reason for use and if the subject anticipates being able to take NSAIDs according to protocol requirements in the future. The discussion should be noted in the patient's source documents. Subjects who indicate that they anticipate being able to take NSAIDs no more than 10 days per 8-week period going forward will be allowed to continue in the treatment period. However, if these subjects continue to take NSAIDs more than 10 days per 8-week period, they should be withdrawn from study treatment and entered into the Early Termination Follow-Up period (See [Section 6.4](#)). Subjects who

indicate they are taking NSAIDs because of insufficient osteoarthritis pain relief or those who indicate they cannot or will not follow the protocol specified restrictions for NSAID use due to any other condition, should be withdrawn from study treatment and entered in the Early Termination Follow-Up period (See [Section 6.4](#)).

Products containing glucosamine sulfate and chondroitin sulfate should not be initiated during the study; however, subjects who have taken a stable dose of these products for at least 6 months prior to the Initial Pain Assessment Period will be allowed to continue their regimen. Herbal, homeopathic, and naturopathic remedies should not be initiated during the study; however, subjects who have taken a stable dose of these products for at least 30 days prior to the Initial Pain Assessment Period will be allowed to continue their regimen. Subjects should be advised that St. John's Wort and other inducers of CYP3A4/5 such as carbamazepine and rifampin may interfere with the efficacy of hormonal contraceptive products. Biologics (for example: TNF- α inhibitors such as adalimumab, etanercept, infliximab) other than study medication, and live attenuated vaccines must not have been taken within 3 months prior to the Initial Pain Assessment Period and are prohibited during the study. Flumist[®] Influenza Virus Vaccine Live, Intranasal or other inhaled influenza vaccines are the only exception of a live attenuated vaccine that will be permitted during the study.

5.7.2. Permitted Treatments

Daily low dose aspirin (≤ 325 mg or per local prescribing practice) therapy for cardiovascular prophylaxis is permitted without restriction.

Medications for other (non-osteoarthritis, non-pain) conditions are permitted provided the subject has received a stable dose for at least 30 days before the IPAP (30 days prior to Screening for antihypertensive medications) and the dose is not expected to change during the study. Note however that dose adjustments (includes starting a new therapy) during the study can be made if required, and recorded on the concomitant medication CRF.

Occasional use of pain medications for pain is permitted in situations such as outpatient diagnostic procedures (eg, colonoscopy, dental procedures) or limited accidental injury (eg, ankle sprains, minor fractures, minor burns/sunburns). Subjects should be counseled to avoid scheduling prospective procedures such that pain medications would be needed within 48 hours of a study visit (24 hours for acetaminophen/paracetamol).

Subjects should be counseled to contact the assigned study monitor or study clinician for guidance/approval regarding the use of prohibited medications for other self-limiting conditions, accidental injury or other surgical procedures as the extent of the condition, injury or procedure and the resulting pain medication usage may require termination from the study. Any use of NSAID must be consistent with the allowed limit described in the Prohibited Medications [Section 5.7.1](#).

For subjects who have discontinued investigational product, the investigator may prescribe standard of care treatment for subjects to take while completing the 24-week Safety Follow-up period once the last efficacy assessments have been obtained at the visit occurring

16 weeks after the last dose of SC investigational product. In this study, standard of care treatment refers to analgesics approved by the relevant Health Authority to relieve the pain of osteoarthritis. These medications include opioids, topical analgesics, NSAIDs, capsaicin products, injectable corticosteroids and viscosupplementation (eg, hyaluronan) and are prescribed at the discretion of the Investigator. Pre-specified analgesics are not considered investigational product but will be reimbursed by Pfizer while the subject is participating in the 24-week Safety Follow-up period after at least 16 weeks have elapsed since their last dose of SC treatment was administered. Their use will be recorded on the concomitant medication CRF.

5.8. Rescue Therapy

Acetaminophen/paracetamol will be issued to the subject by the study sites in its approved marketed product dress (carton, bottle, documents) for use as rescue medication.

During the Washout period and the Initial Pain Assessment Period, subjects may take rescue medication (acetaminophen/paracetamol) as needed for osteoarthritis or other types of pain or illness up to a maximum daily dose of 4000 mg/day, or as permitted by local or national labeling. Rescue medication must be discontinued at least 24 hours prior to the Baseline (Day 1) visit.

In the event of inadequate pain relief for osteoarthritis during the Double-blind Treatment period (between the Baseline [Day 1] visit and Week 24), subjects may take up to a maximum permitted daily dose of 4000 mg but only up to 5 days per week, or as permitted by local or national labeling.

From the Baseline (Day 1) visit through Week 24, subjects taking rescue medication greater than 5 days per week (any level of acetaminophen/paracetamol used specifically for osteoarthritis pain) must be interviewed by study site personnel to determine if this is due to lack of efficacy or other reasons, and the discussion should be noted in the subject's source documents. Subjects who have taken rescue medication more frequently than specified in the protocol during the treatment period due to lack of efficacy and indicate that they cannot or will not follow the rescue medication protocol requirements because of insufficient osteoarthritis pain relief should be withdrawn from investigational product due to lack of efficacy and entered in the Early Termination Follow-up period (refer to [Section 6.4](#)). Subjects who indicate that they anticipate being able to take rescue medication no more than 5 days per week going forward will be allowed to continue in the treatment period. However, if these subjects continue to take rescue medication more than 5 days per week, they should be withdrawn from investigational product and entered into the Early Termination Follow-up period (refer to [Section 6.4](#)).

Between the Week 24 and Week 32 visits, subjects may take acetaminophen/paracetamol rescue medication daily, up to the maximum permitted dose of 4000 mg per day, or as permitted by local or national labeling. After the Week 32, subjects may be started on standard of care treatments for osteoarthritis pain. Subjects may continue to use acetaminophen/paracetamol as needed up to the maximal permitted dose of acetaminophen per day as permitted by local or national labeling.

During the Early Termination Follow-up period (described in [Section 6.4](#)), up to 16 weeks after the last dose of SC investigational product, subjects may take acetaminophen/paracetamol rescue medication up to the maximum permitted dose of 4000 mg/day, or as permitted by local or national labeling. After Early Termination Visit 2 (approximately 16 weeks after the last dose of SC investigational product) subjects may be started on standard of care treatments for osteoarthritis pain. Subjects may continue to use acetaminophen/paracetamol as needed up to the maximal permitted dose of acetaminophen/paracetamol per day per local or national labeling.

All rescue medication must be discontinued at least 24 hours prior to any scheduled study visit at which efficacy data is collected (ie, up to the Week 32 visit that occurs 16 weeks after the last dose of SC investigational product).

Subjects should bring back rescue medication bottles at each study visit for assessment of compliance.

Subjects will be instructed that many over-the-counter medications contain acetaminophen/paracetamol, and to guard against overuse. Subjects will be instructed to record their acetaminophen/paracetamol rescue medication usage daily via IRT through Week 24. After Week 24 and through the Week 48 visit, usage of acetaminophen/paracetamol rescue medication will be recorded once weekly via the IRT. The dose and reason for acetaminophen/paracetamol use in instances other than as rescue medication (eg, toothache, headache, fever) must be recorded on the appropriate concomitant medication CRF.

6. STUDY PROCEDURES

Refer to Schedule of Activities ([Tables 1 and 2](#)) for the lists of procedures to be performed throughout the study.

If possible, each subject's clinic visit should be conducted at approximately the same time of day throughout their participation in the study. As a general rule, scales/instruments should be completed first by the subject upon arrival at the clinic and vital signs should be assessed prior to blood draws at clinic visits.

Subjects should be thoroughly instructed on completion of the scales/instruments via IRT prior to completing them the first time (eg at Screening for WOMAC Pain subscale and Numeric Pain Scale Rating; at Baseline for Patient Global Assessment (PGA) of Osteoarthritis, EQ-5D-5L, WPAI:OA, mPRTI questionnaires). No coaching or other interpretative assistance should be given to subjects during completion of these questionnaires.

Continuing on from the Initial Pain Assessment Period, subjects will provide a daily assessment of their index joint pain through Week 24 via IRT (though these assessments could begin as early as at the Screening Visit). Between Weeks 24 and 48 (End of Study / Early Termination), subjects will provide pain scores in the index joint weekly via IRT using a 24-hour recall period. Subjects will also provide a weekly assessment of their non-index

joint (major joints, refer to [Section 7.1.1](#)) pain via IRT using a 24-hour recall period from the Initial Pain Assessment Period to Week 48. The use of rescue medication will be collected daily via IRT beginning in the IPAP (though collection of rescue medication use could begin as early as at the Screening Visit) to the Week 24 visit and then weekly until Week 48. On a weekly basis between Baseline and Week 48, subjects will record the number of days of concomitant NSAID use via IRT.

Study visit windows are ± 3 days for Weeks 2 and 4, and ± 7 days for Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48. Study visits should be scheduled with reference to the original baseline visit date as much as possible. Subject scheduling issues should be brought to the attention of the assigned study monitor or study clinician for resolution. Dosing visits should occur no earlier than 7 weeks from the previous injection. Visit window for the Week 48 (End of study) X-rays is ± 30 days from the nominal time point of the visit; however they should preferably be obtained prior to the Week 40 visit and, if possible, less than 14 days after the visit.

Subjects will be reminded to abstain from taking rescue medication 24 hours prior to any study visit at which efficacy data is collected.

6.1. Screening

The Screening period will consist of a maximum of 37 days prior to Randomization. Prior to entering the Initial Pain Assessment Period (IPAP; see [Section 6.1.3](#)), subjects taking prohibited medications must complete the required washout from these medications for at least 5 half-lives or 48 hours (whichever is greater). Screening procedures should be staged to minimize burden to the subject and to minimize conduct of procedures that may not be required if a subject is found to be ineligible.

Written informed consent will be obtained from each subject prior to any trial assessments. Each subject will be assessed as to his/her suitability per inclusion/exclusion criteria review.

Subject demographics and the date of OA diagnosis for every affected joint will be obtained. A comprehensive medical history and concomitant medication review will be performed for each subject.

History of insufficient pain relief from, inability to tolerate or contraindication to taking, acetaminophen/paracetamol, NSAID, and tramadol or opioid treatments will be clearly documented on the appropriate CRF page. The required level of evidence to establish that subjects meet this inclusion criterion will be based upon the investigator's judgment. Investigators should rely upon available medical records that he or she may already have access to, prescription medication records (eg, retail pharmacy records), records or information provided by referring physicians and/or subject historical recall if the investigator is satisfied with the level of detail subjects are able to provide on past medication use. Investigators should clearly document in source records the information used to establish whether a subject does or does not meet this inclusion criterion. As a guide, investigators should document medication names, medication doses, reasons for use, dates of use and reason for discontinuation. If one or more of the above medications could not be

used due to contraindication or if the subject refuses to take the medication due to fear of known side effects, this should also be clearly documented with supporting detail.

NOTE: *In Japan, Investigators will also need to document the outcome of a trial of acetaminophen.*

In addition, a comprehensive evaluation of musculoskeletal history and musculoskeletal physical exam will be performed (refer to [Section 7.3.1.2](#)). The index joint (hip or knee) will be selected at Screening. If bilateral knee and/or hip pain is present, the investigator will select the more painful joint as the study (index) joint. X-ray confirmation of eligibility (Kellgren-Lawrence grade ≥ 2 for selected index joint and absence of exclusionary conditions) will be obtained from the imaging Central Reader based on the radiographs of each knee, hip and shoulder (and any other major joints imaged at) at Screening. Screening X-rays should be obtained as early as possible in the Screening period to facilitate completion of all required procedures within the 37-day Screening period and anticipate that it may take up to 2 weeks to obtain X-ray confirmation from the Central Reader.

Other major joints exhibiting signs or symptoms suggestive of osteoarthritis should also be imaged and will also be reviewed by the imaging Central Reader. A major joint is defined as a mobile synovial joint in the limbs such as shoulders, elbows, wrists, hips, knees, ankles and excluding the joints of the toes and hands. During Screening, subjects will also provide a pain score (scored with an 11-point numerical rating scale [NRS]) via Interactive Response Technology (IRT) for any other major joint for which a radiograph is obtained (refer to [Section 7.3.3](#)).

6.1.1. Screening Period:

- Informed consent.
- Demographics and general medical history.
- Assessment of depression by medical history (Use of PHQ-9 is optional and suggested as a tool to assess seriousness of depression if needed. If the PHQ-9 is utilized, the completed questionnaire should be archived in the subject's source documents.).
- Numeric Pain Scale rating (IRT) for major joints (bilateral shoulders, hips and knees) and any painful joint imaged at Screening.
- Primary diagnosis and selection of index hip or knee.

NOTE: If the subject experiences pain in more than one joint, then the most painful joint should be selected as the index joint. Radiographic eligibility of the selected index joint will need to be confirmed by the Central Reader.

- WOMAC (all subscales via IRT) for index hip or knee.

NOTE: Subjects should be thoroughly instructed on completion of WOMAC scales, and no coaching or other interpretative assistance should be given to subjects during completion of these questionnaires.

- Comprehensive musculoskeletal/joint related medical history (includes past history of osteoarthritis, osteoporosis, osteopenia, joint pain, injury, trauma, joint surgeries (including arthroscopic procedures), ligament tear or rupture, fractures, gout, joint injuries or other conditions).
- Medication history (record any use of medications for osteoarthritis, prior 30 day use for all other medications).
- Weight and Height with BMI calculation, Smoking Status, Alcohol Use/Dependency, Female Hormonal Status (if known or pending laboratory results).
- Vital signs after sitting for at least 5 minutes, (blood pressure, and heart rate).
- Orthostatic blood pressure (supine / standing) measurement.
- General physical examination.
- Musculoskeletal physical examination.
- Neurologic exam/Neuropathy Impairment Score.
- Survey of Autonomic Symptoms (SAS) questionnaire.
- ECG (12-lead).
- X-rays of each knee, hip and shoulder (and any other painful, major joint if appropriate).
- Clinical laboratory tests (blood chemistry, hematology, and urinalysis, serum Hepatitis B, C, and HIV screen, urine toxicology screen, HbA1c), serum pregnancy testing/FSH testing if needed.

NOTE: Clinically significant abnormal laboratory tests (except urine toxicology screen) or tests not meeting inclusion/exclusion criteria may be repeated for verification prior to Baseline. Refer to [Section 7.3.2](#) for specific instructions related to laboratory screening tests.

- Inclusion/exclusion review (pending results of laboratory tests, ECG and X-rays). If a subject qualifies other than pending results they may begin the washout of prohibited pain medications (refer to [Section 5.7.1](#) and [Appendix 3](#)). Subjects who are found to be ineligible subsequent to the receipt of disqualifying laboratory, ECG or X-ray results may be asked to return requested study related materials and will exit the Screening period (Screen Failure).

- Female subjects of child-bearing potential will be instructed on the contraception requirements for this study; the investigator or designee will confirm that female subjects of child-bearing potential have selected 2 highly effective or acceptable forms of contraception from the list of acceptable methods and instruct the subject in their consistent and correct use. The conversation will be documented in the subject chart.

***NOTE:** In Japan, only female subjects who are not of childbearing potential will be eligible for this study.*

***NOTE:** In Sweden, the investigator or designee will confirm that female subjects of child-bearing potential have selected 1 highly effective form of contraception from the list of acceptable methods and instruct the subject in their consistent and correct use. The conversation will be documented in the subject chart.*

- Dispense Screening period rescue medication; subjects will be instructed on the permissible amounts of rescue medication during the washout period, during the IPAP and during the treatment period, as well as the need to refrain from rescue medication use at least 24 hours prior to a study visit (refer to [Section 5.8](#)).
- Subjects will be instructed in the use of the IRT system to record daily/weekly pain ratings, rescue medication use and any NSAID use, with specific instructions as when to test the system and when to begin entering data;
- Subjects in Japan who have not had a trial of acetaminophen (as monotherapy or in combination with tramadol) for their osteoarthritis, will undergo at least a 1-week trial of an approved daily dose of acetaminophen after obtaining informed consent because subjects are required to have documentation that acetaminophen has not provided sufficient pain relief. If they obtain sufficient response to acetaminophen, as judged by the subject and Investigator, they will then be withdrawn from the study. Those who do not have a sufficient response to acetaminophen will continue with the screening process. Subjects who have not achieved an adequate response to an approved dose of Tramacet® (1 - 2 tablets four times a day (QID): total daily tramadol 150 mg - 300 mg and acetaminophen 1300 mg - 2600 mg) can be considered to meet the acetaminophen and tramadol inclusion criterion.
- Subjects who are found to be ineligible may be asked to return requested study related materials and will exit the Screening period (Screen Failure);
- Subjects who do not require a washout of prohibited pain medications may begin the Initial Pain Assessment Period, preferably once X-ray confirmation of radiographic eligibility of the subject has been received from the Central Reader.

6.1.2. Washout Period

The beginning of the Washout Period will preferably be scheduled based on the planned start of the Initial Pain Assessment Period so as to minimize the time spent without analgesic medications prior to Randomization. The Washout Period will include the discontinuation

and washout of all prohibited medications for at least 5 half-lives or 48 hours (whichever is greater) prior to the Initial Pain Assessment Period (the 7 days prior to randomization) and will be a minimum of 2 days for all prohibited pain medications (Refer to [Appendix 3](#)). Subjects experiencing pain during the Washout Period may take acetaminophen as needed up to 4000 mg per day, but must discontinue rescue medication for at least 24 hours prior to the Baseline (Randomization) Visit. However, the total duration of the Screening period is not to exceed 37 days.

6.1.3. Initial Pain Assessment Period (IPAP)

The IPAP will begin 7 days prior to the Baseline (Day 1) randomization visit, and subjects must complete at least 3 diary entries during the IPAP period, but all diary entries will be used to determine the baseline value for the average pain score in the index joint.

- During this time, subjects will record daily pain scores for their index joint (knee or hip) and rescue medication use via the IRT (refer to [Sections 7.1.1](#) and [Section 7.1.2](#)). Assessment of the non-index joints will be performed once during the IPAP.

NOTE: Study sites will monitor the IRT reports for compliance with diary recordings and rescue medication use and reschedule those subjects who fail to provide 3 diary days or fail to refrain from rescue medication use 24 hours prior to Baseline.

6.2. Double-Blind Treatment Period

The Double-blind Treatment period begins with the Baseline (Day 1) visit and concludes with completion of the Week 24 visit procedures. The Double-blind Treatment period is 24 weeks in duration and consists of 7 clinic visits (Day 1 and Weeks 2, 4, 8, 12, 16 and 24) and 1 telephone contact (Week 20) between site staff and study subjects.

6.2.1. Baseline (Day 1) Clinic Visit

6.2.1.1. Assessment of Randomization Criteria and Randomization

Subjects must continue to satisfy Inclusion/Exclusion Criteria [general criteria and those specific to the Baseline (Day 1) visit – refer to [Section 4.3](#)] to be eligible for Randomization. Full eligibility, including (but not limited to) confirmation of appropriate washout of concomitant medication, abstinence from acetaminophen/paracetamol in the previous 24 hours, completion of at least 3 diary entries in the past 7 days, required WOMAC Pain and Physical Function subscale and Patient's Global Assessment of Osteoarthritis scores, and that no adverse events occurred since signing informed consent that would render the subject ineligible for randomization, should be assessed before carrying out randomization in the IRT system.

Subjects will undergo the following assessments prior to randomization:

- Inclusion/exclusion review (including results of ECG, laboratory and X-rays obtained at the Screening visits).
- WOMAC (all subscales).

- Patient's Global Assessment of Osteoarthritis.

NOTE: Subjects should be thoroughly instructed on completion of Patient's Global Assessment of Osteoarthritis questionnaires, no coaching or other interpretative assistance should be given to subjects during completion of these questionnaires.

- Musculoskeletal physical examination.
- Vital signs after sitting for at least 5 minutes, (blood pressure, and heart rate).
- Orthostatic blood pressure (supine/standing) measurement.
- Review of concomitant medication.
- Rescue medication (acetaminophen/paracetamol) review.
- Instruction/review of subject compliance with daily/weekly assessments and operation of the IRT.
- Confirm with females of child bearing potential that they understand and are willing to follow the contraceptive requirements.
- Adverse events that occurred after signing the Informed Consent Document (pretreatment adverse events).
- Urine pregnancy test for females of childbearing potential (must be negative).

6.2.1.2. Randomization

Subjects satisfying eligibility requirements will be randomized via an IRT system. The randomization number assigned to the subject will be provided by the system. Subjects satisfying eligibility requirements will undergo the following assessments prior to the first dose of investigational product.

6.2.1.3. Pre-dosing (Day 1)

Randomized subjects will undergo the following assessments prior to the first dose of investigational product. Some of these may be performed prior to randomization for convenience:

- WPAI:OA.
- EQ-5D-5L.
- Assessment of Health Care Resource Utilization.
- Neurologic exam/Neuropathy Impairment Score.

- Clinical laboratory tests (blood chemistry and hematology).
- Serum and plasma retention samples.
- Blood sample for anti-tanezumab antibody assessment (refer to [Section 7.3.9](#)).
- Blood samples for pharmacokinetics (PK) and pharmacodynamics (PD) (NGF) analyses (refer to [Section 7.5](#)).
- Blood and urine samples for biomarkers (fasting if possible, urine sample should be from 2nd void of the day or after; refer to [Section 7.6](#)).
- Blood sample for banked biospecimens (see [Section 7.7.1](#) Markers of Drug Response and Other Additional Research, [Section 7.7.2](#)).
- Dispense rescue medication.
- Female subjects of child-bearing potential to be reminded of contraceptive requirements.

6.2.1.4. Dosing (Day 1)

Subjects will receive a single SC injection of blinded investigational product according to the treatment assigned by the IRT system (refer to [Section 5](#)).

The administration of investigational product must be performed by trained medical staff and where facilities to handle allergic reactions are available. Should a subject experience symptoms typical of an allergic reaction, then investigational product administration should be discontinued permanently. Subjects will receive appropriate treatment such as corticosteroids or antihistamine at the discretion of the Investigator. No other dosage modifications are allowed.

6.2.1.5. Post-dosing (Day 1)

Subjects will be observed in the clinic for at least 1 hour after dosing. The following procedures will be completed at approximately 1-hour post-dose:

- Review and record adverse events.

Each subject should be reminded to seek medical care and/or contact the Investigator if the subject experiences symptoms of an acute or severe hypersensitivity reaction (eg, shortness of breath, anaphylaxis, urticaria, angioedema) after leaving the clinic.

6.2.2. Routine Clinic Visits (Week 2, Week 4 and Week 12)

The subject will return for clinic visits at Week 2, Week 4 and Week 12 to be assessed for efficacy and safety. Refer to Schedule of Activities ([Table 1](#)) for the procedures to be performed at the Week 2, Week 4 and Week 12 Visits.

6.2.3. Dosing Visits (Week 8 and Week 16)

The subject will return for clinic visits at Week 8 and at Week 16 to be assessed for efficacy and safety. At Week 8 and Week 16 the subject will receive the second and third administrations of SC investigational product, respectively. Refer to Schedule of Activities ([Table 1](#)) for the procedures to be performed at the Week 8 and Week 16 Clinic Visits. The dosing and post-dosing procedures are the same as those as described in [Sections 6.2.1.4](#) and [Section 6.2.1.5](#).

6.2.4. Phone Contact Visit (Week 20)

The subject will be contacted by telephone at Week 20 to review adverse events, concomitant medications, compliance with daily/weekly IRT entries and to remind female subjects of contraceptive requirements.

Refer to Schedule of Activities ([Table 1](#)) for the procedures to be performed at the Week 20 Phone Contact. At the time of this phone contact visit, reminder to schedule Week 24 X-rays to occur within the window for Week 24 X-rays.

6.2.5. Week 24 Clinic Visit (End of Double-Blind Treatment)

The subject will return for a clinic visit at Week 24 to be assessed for efficacy and safety. Refer to Schedule of Activities ([Table 1](#)) for the procedures to be performed at Week 24 Clinic Visit and [Section 7](#) for more details on these procedures.

With the completion of the Week 24 visit, the subject will begin the 24-week Safety Follow-up Period.

6.3. Safety Follow-up Period

The Safety Follow-up period begins once the Week 24 procedures have been completed and concludes with completion of the Week 48 visit procedures. The Safety Follow-up period is 24 weeks in duration and consists of 2 clinic visits (Weeks 32 and 48) and 4 telephone contacts (Weeks 28, 36, 40 and 44) between site staff and enrolled subjects.

6.3.1. Phone Contact Visits (Weeks 28, 36, 40 and 44)

The subject will be contacted by telephone at Weeks 28, 36, 40 and 44 to review adverse events, concomitant medications, compliance with weekly IRT entries and to remind female subjects of contraceptive requirements (Week 28 only).

At the Week 44 phone contact visit, schedule Week 48 X-rays, to occur preferably prior to the nominal time point of the Week 48 visit and if possible, no more than 14 days after the Week 48 visit.

Refer to Schedule of Activities ([Table 1](#)) for the procedures to be performed at the Weeks 28, 36, 40 and 44 Phone Contact.

6.3.2. Routine Clinic Visit (Week 32)

The subject will return for a clinic visit at Week 32 to be assessed for efficacy and safety. Refer to Schedule of Activities ([Table 1](#)) for the procedures to be performed at the Week 32 Visit.

Once the clinic visit has been completed and final efficacy assessments have been collected, standard of care treatment can be offered to subjects who intend to complete the remaining 16 weeks of the required Safety Follow-up period. In this study, standard of care treatment refers to analgesics approved by the relevant Health Authority to relieve the pain of osteoarthritis. Standard of care treatment may be initiated as needed and should be recorded on the concomitant medication CRF.

6.3.3. Week 48 Clinic Visit (End of Study)

The subject will return for a clinic visit at Week 48 to be assessed for safety. Week 48 is the End of Study Visit. Refer to Schedule of Activities ([Table 1](#)) for the procedures to be performed at the Week 48 (End of Study) Clinic Visit.

If not already completed, schedule subject for follow-up radiographic assessments (X-rays) of bilateral shoulders, hips and knees and any other joint for which a radiograph was obtained at the Screening visit or any at risk joint identified during the study period (refer to [Section 7.3.7](#)).

6.4. Subject Withdrawal / Early Termination

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The Investigator should inquire about the reason for withdrawal, follow-up with the subject regarding any unresolved adverse events and request that the subject return for follow-up visits as indicated in the schedule below. Subjects of child-bearing potential should be reminded to continue contraceptive measures at least 112 days (16 weeks) after the last dose of investigational product.

Subjects discontinuing from treatment (prior to Week 24), either at their request or at the decision of the investigator, will be required to undergo 24 weeks of post-treatment follow-up (as described in [Section 6.4.1](#)). The 24 weeks of follow-up will be obtained through 3 clinic visits and 2 phone calls to yield 24 weeks of follow-up, as described in [Section 6.4.1](#). In addition, subjects will be asked to continue to enter pain scores for index and non-index joint pain scores and for major joints via IRT, weekly, until 24 weeks after the subject's last dose of SC study treatment to the end of the 24-Week Safety Follow-up period.

In the event a subject refuses the Early Termination safety follow-up, or chooses to discontinue during the safety follow-up (after Week 24 and through Week 48), a complete early termination visit should be performed that should include all procedures described in [Section 6.4.1.1](#). Early Termination 1 (also described in [Table 2](#) column 3), including the X-rays of major joints provided at least 30 days have elapsed since the last X-rays were collected (see [Section 6.4.1](#). and [Table 2](#) column 2). In addition, female subjects will be advised to continue their contraception regimen during a period of 112 days (16 weeks) after the last dose of SC investigational product.

Withdrawal of Consent: Subjects who request to discontinue study treatment will remain in the study and will continue to be followed for protocol specified follow-up procedures unless they specifically withdraw consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. Pfizer may retain and continue to use any data collected before such withdrawal of consent.

Lost to Follow-Up: All reasonable efforts must be made to locate subjects as to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented contacts (via phone calls, faxes, and/or emails) as well as lack of response by subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

Brief summary of procedures for subjects discontinuing from study treatment

X-rays of the knee, shoulder and hip (and any other joint imaged at Screening or identified as at risk during the study) should be performed as soon as possible after the decision to withdraw from the study has been made, provided at least 30 days have passed since the last set of X-rays were collected (refer to [Section 6.4.1](#).).

The remainder of efficacy and safety assessments should be done at the scheduled first visit which is to occur approximately 8 weeks after the last dose of SC study treatment (refer to [Section 6.4.1.1](#), Early termination Visit 1). The site should also schedule the subject for two additional clinic visits. The second visit should be scheduled to occur approximately 16 weeks after the subject's last dose of SC study treatment (which corresponds to more than 5 times the elimination half-life of tanezumab) to collect safety and efficacy data (refer to [Section 6.4.1.3](#), Early Termination Visit 2). Once the clinic visit 16 weeks after the last administration of SC study treatment has been completed and final efficacy assessments have been collected, standard of care treatment may be offered to subjects who are completing the remaining 8 weeks of the required follow-up period. The third and final clinic visit should be scheduled to take place approximately 24 weeks after the subject received the last dose of SC study treatment (refer to [Section 6.4.1.4](#), Early Termination Visit 3). Telephone contact will be made with subjects at approximately 12 and 20 weeks following the last SC dose of study treatment. Every effort should be made to have the subject agree to complete the entire 24-week Early Termination Safety Follow-up described in [Section 6.4.1](#).

6.4.1. Early Termination Follow-Up Procedures

As soon as possible following a decision to withdraw a subject from the study is made, provided at least 30 days have passed since the last set of X-rays were collected, X-rays of all joints for which X-rays were obtained at Screening and other at risk joint identified during the study period should be obtained (refer to [Section 7.3.7](#)). X-rays should be submitted to imaging central reader.

Refer to the Early Termination Schedule of Activities ([Table 2](#)).

6.4.1.1. Early Termination Visit 1 (~8 weeks after last dose of SC investigational product)

Refer to the Early Termination Schedule of Activities ([Table 2](#)) and [Section 7](#) for information on the procedures to be performed at Early Termination Visit 2.

6.4.1.2. Early Termination Telephone Contacts 1 and 2 (~12 weeks and ~20 weeks after last dose of SC investigational product)

The subject will be contacted by telephone twice (~12 weeks and ~20 weeks after the last dose of SC investigational product) to review adverse events, concomitant medications, compliance with daily/weekly IRT entries and to remind female subjects of contraceptive requirements.

Refer to the Early Termination Schedule of Activities ([Table 2](#)) for the procedures to be performed at the Early Termination Telephone Contacts.

At Telephone Contact 2, schedule Week 24 X-rays, to occur preferably prior to the nominal time point of the visit but if possible, no more than 14 days after the Early Termination Visit 3.

6.4.1.3. Early Termination Visit 2 (~16 weeks after last dose of SC investigational product)

Refer to the Early Termination Schedule of Activities ([Table 2](#)) and [Section 7](#) for information on the procedures to be performed at Early Termination Visit 2.

6.4.1.4. Early Termination Follow-up Visit 3 (~24 weeks after last dose of SC investigational product)

Refer to the Early Termination Schedule of Activities ([Table 2](#)) and [Section 7](#) for information on the procedures to be performed at Early Termination Visit 3.

6.4.2. Procedures for Subjects Undergoing Joint Replacement

Subjects who have undergone or plan to undergo total joint replacement or other arthroplasty procedure during the study will be discontinued from investigational product.

Subjects who undergo total knee, hip or shoulder joint replacement surgery during the study (Double-blind Treatment Period or Follow-up Period) will be followed for 24 weeks after the procedure as part of a separate protocol (Study A4091064), provided the subject consents.

Transition procedures into Study A4091064 are determined by the timing of total joint replacement surgery:

- Subjects who have undergone or plan an immediate total knee, hip or shoulder joint replacement will be discontinued from the Double-Blind Treatment period and enter into the total joint replacement follow-up protocol (Study A4091064). At the discontinuation visit, all procedures scheduled for the Week 24 and Week 32 visits should be completed unless the Subject has already completed the Week 24 and Week 32 visits, in which case only Week 48 procedures will be required. In addition, if the Week 24 visit was not completed prior to termination, a general physical examination, body weight, WPAI:OA, EQ-5D-5L and mPRTI will also be obtained. Applicable Study A4091064 Baseline Visit activities should be completed on the same day as the Study A4091057 End of Treatment Visit.
- Subjects who plan to undergo total knee, hip or shoulder joint replacement during the study will be discontinued from the Double-blind Treatment Period and entered into Early Termination Follow-up (See [Section 6.4](#)) until their joint replacement procedure. For these subjects, a complete early termination visit should be conducted prior to the total joint replacement (See [Section 6.4](#)) and entrance into Study A4091064. Study A4091064 Baseline Visit activities should be completed on the same day as the Study A4091057 early termination visit. Subjects who have not undergone or scheduled total joint replacement surgery within the study treatment period or safety follow-up period of this study will not be eligible for Study A4091064.

Subjects who undergo other types of joint replacement surgery or arthroplasty during the study should be discontinued from investigational product and complete the protocol specified Safety Follow-up Period, but are not eligible for entry into Study A4091064.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Subject Diary Assessments

7.1.1. Daily / Weekly Pain Assessments

If possible diary assessments of pain in the index joint and assessment of the major non-index joints will be completed by the subject at approximately the same time each day (or each week). Average pain will be assessed with an 11-point Numeric Rating Scale (NRS) ranging from zero (no pain) to 10 (worst possible pain) captured through IRT. The subjects should describe their pain in the index joint (and non-index joint when applicable) during the past 24 hours by choosing the appropriate number from 0 to 10. If possible, subjects should conduct the self-assessment in the evening.

Index Joint Pain Assessment

Average pain in the index joint will be assessed by the subject daily from the beginning of the IPAP to the Week 24 Visit, followed by weekly beginning after the Week 24 visit through Week 48 (and weekly during the Early Termination Follow-Up Period, if applicable).

- Example question when the identified index joint is the right knee:

“Select the number that best describes your average pain in your index joint, the right knee in the past 24 hours”:

0 1 2 3 4 5 6 7 8 9 10

No
Pain

Worst Possible
Pain

- Example question when the index joint is the right hip:

“Select the number that best describes your average pain in your index joint, the right hip in the past 24 hours”:

0 1 2 3 4 5 6 7 8 9 10

No
Pain

Worst Possible
Pain

Non-index Joint Pain Assessment

On a weekly basis beginning at the Initial Pain Assessment Period and through Week 48 of the study (and weekly during the Early Termination Follow-Up Period), subjects will also be asked if he/she experienced new onset or increased pain in any major non-index joint. A major joint is defined as a mobile synovial joint in the limbs such as shoulders, elbows, wrists, hips, knees, ankles and excluding the joints of the toes and hands. If a subject responds that he/she has experienced new onset or increased pain in a non-index joint or other major joint (post-baseline), the subject will be asked to rate his/her pain in that joint on the same 11-point numeric rating scale shown above and will be asked to rate his/her pain in that joint for the remainder of the study.

7.1.2. Rescue Medication and Amount

Rescue medication use will be collected daily via IRT from the beginning of the IPAP to the Week 24 Visit. The dosage strength of the acetaminophen/paracetamol tablets/caplets/capsules will be captured. The subject should note the number of tablets/caplets/capsules of rescue medication taken during the last 24 hours.

Following the Week 24 visit up to the Week 48 visit and during the Early Termination Follow-Up Period for subjects who enter this phase of the study, the use of acetaminophen / paracetamol as rescue medication will be collected once weekly using IRT. The subject will record the number of days when rescue medication was used and maximum number of tablets, capsules or caplets of rescue medication taken on any day in the past week.

7.1.3. Concomitant NSAID Use

Use of over-the-counter or prescription NSAID will be collected weekly via IRT from the Baseline (Day 1) visit until the Week 48 visit. During the Early Termination Follow-Up Period for subjects who enter this phase of the study, the use of over-the-counter or prescription NSAID will be collected once weekly using IRT. Subjects will record the number of days of NSAID use in the past week using IRT. At telephone or clinic visits, sites will interview the subject regarding their NSAID use and record additional information on a CRF, such as the medication name, dosage and reason for use. The investigator or designee should closely monitor for concomitant NSAID use. Subjects reporting concomitant NSAID use will be managed per guidance provided in [Section 5.7.1](#).

7.2. Study Visit Efficacy Assessments

For the timings of procedures, refer to Schedule of Activities ([Tables 1 and 2](#)).

7.2.1. Western Ontario and McMaster Universities Osteoarthritis Index

A copy of the WOMAC¹⁹ Osteoarthritis NRS Index is provided in [Appendix 4](#). The WOMAC subscales will be recorded via IRT at relevant study visits.

7.2.1.1. WOMAC Pain Subscale

At Screening and for the remainder of a subject's participation in the study, a WOMAC pain subscale questionnaire will only be completed for the index knee or hip.

The WOMAC Pain subscale is comprised of 5 questions regarding the amount of pain experienced due to osteoarthritis in the index joint (selected study knee or hip) in the past 48 hours. The WOMAC Pain subscale is calculated as the mean of the scores from the five individual questions, which may not be a whole (integer) number. The WOMAC Pain subscale NRS scores for each question, and the WOMAC Pain subscale score, range from 0 to 10, with higher scores indicating higher pain.

7.2.1.2. WOMAC Physical Function Subscale

At the Baseline (Day 1) visit and for the remainder of a subject's participation in the study, a WOMAC Physical Function subscale questionnaire will only be completed for the index knee or hip.

The WOMAC Physical Function subscale is comprised of 17 questions regarding the degree of difficulty experienced due to arthritis in the index joint (selected knee or hip) in the past 48 hours. The WOMAC Physical Function subscale is calculated as the mean of the scores from the seventeen individual questions, which may not be a whole (integer) number. The WOMAC Physical Function subscale NRS scores for each question, and the WOMAC Physical Function subscale score, range from 0 to 10 with higher scores indicating worse function. This refers to the subject's ability to move around and perform usual activities of daily living.

7.2.1.3. WOMAC Stiffness Subscale

At the Baseline (Day 1) visit and for the remainder of a subject's participation in the study, a WOMAC Stiffness subscale questionnaire will only be completed for the index knee or hip.

The WOMAC Stiffness subscale is comprised of 2 questions regarding the amount of stiffness experienced in the index joint in the past 48 hours. The WOMAC Stiffness subscale is calculated as the mean of the scores from the two individual questions, which may not be a whole (integer) number. The WOMAC Stiffness subscale NRS scores for each question, and the WOMAC Stiffness subscale score, range from 0 to 10 with higher scores indicating more stiffness. Stiffness is defined as a sensation of decreased ease with which the subject moves the index knee or hip.

7.2.2. Patient's Global Assessment of Osteoarthritis

At the Baseline (Day 1) visit and for the remainder of a subject's participation in the study, a Patient's Global Assessment of Osteoarthritis questionnaire will only be completed for the index knee or hip ([Appendix 5](#)).

Subjects who have a knee as index joint will answer the following question: "Considering all the ways your osteoarthritis in your knee affects you, how are you doing today?"

Subjects who have a hip as index joint will answer the following question: "Considering all the ways your osteoarthritis in your hip affects you, how are you doing today?"

Subjects will rate their condition using the following scale:

| Grade | Description |
|---------------|---|
| 1 – Very Good | Asymptomatic and no limitation of normal activities |
| 2 – Good | Mild symptoms and no limitation of normal activities |
| 3 – Fair | Moderate symptoms and limitation of some normal activities |
| 4 – Poor | Severe symptoms and inability to carry out most normal activities |
| 5 – Very Poor | Very severe symptoms which are intolerable and inability to carry out all normal activities |

7.2.3. Work Productivity and Activity Impairment Questionnaire - Osteoarthritis – Knee or Hip v2.0 (WPAI:OA)

The WPAI-OA Knee or Hip is a 6-item validated questionnaire that assesses the impact of osteoarthritis on absenteeism, presenteeism, work productivity, and activity impairment.²⁰ Each subscale score is expressed as an impairment percentage (0-100) where higher numbers indicate greater impairment and less productivity. The WPAI-OA is self-administered by the subject and takes less than 5 minutes to complete ([Appendix 6](#)).

7.2.4. EuroQol 5 Dimension (EQ-5D-5L)

The EQ-5D-5L™ is a subject completed questionnaire designed to assess the subject's current health and translate that score into an index value or utility score. Health status is described in terms of 5 dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. There are two components to the EQ-5D-5L™: a Health State Profile and a visual analog scale (VAS) item. The 5 item health state profile will be assessed to calculate a single index value (see [Appendix 7](#)). This instrument provides a mechanism for conducting cost-effectiveness and cost-utility analyses.²¹

7.2.5. Patient Reported Treatment Impact Assessment-modified (mPRTI)

The mPRTI is a self-administered questionnaire containing four items to assess subject satisfaction, previous treatment, preference and willingness to continue using the investigational product. Higher scores indicate greater satisfaction, preference or willingness to use the investigational product; see [Appendix 12](#). Subjects will record their responses

using IRT.

7.2.6. Assessment of Health Care Resource Utilization of Healthcare Resources Assessment

The utilization of health care resources (eg doctor office visits, hospitalizations, surgeries, or procedures, etc.) during the 3 months prior to Baseline will be assessed by questionnaire at Baseline (Day 1), Week 32 and Week 48, and also at Early Termination Visits 2 and 3 (Tables 1 and 2). Subjects will record their responses using IRT.

7.3. Safety Assessments

For the timings of procedures, refer to Schedule of Activities (Tables 1 and 2).

Each subject will provide a general medical history as well as a detailed musculoskeletal/joint specific medical history. The information will be recorded on the appropriate CRF(s) at Screening. Information on prior medications (within 30 days of the Screening Visit for non-analgesic medications, any used for pain and other medications for the treatment and relief of symptoms of osteoarthritis), non-pharmacologic therapies, supplements and concomitant medication use will be collected at Screening and concomitant medication at each scheduled study visit. Information regarding tobacco and alcohol use and dependency will also be collected at Screening.

7.3.1. Physical Examination

7.3.1.1. General Physical Examination

Each subject will undergo a general physical examination.

7.3.1.2. Musculoskeletal History and Physical Examination

At Screening, the investigator should collect a thorough musculoskeletal history. The investigator should inquire about current and past history of osteoarthritis, ligament tear or rupture, joint surgeries (including arthroscopic procedures), fractures, gout, osteoporosis, osteopenia, joint injuries or other conditions.

At each visit, the investigator will conduct a thorough musculoskeletal physical examination of all major joints. The musculoskeletal physical examination should evaluate the joints for swelling, redness, tenderness, deformity, osteophytes or nodes, crepitus and pain on motion and will be documented on the CRF. The investigator should also collect subject-reported information on any current joint symptoms including pain, stiffness, and swelling. Any clinically significant change in symptoms or the examination should be reported as an adverse event.

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7.3.2. Laboratory Safety Assessments

Blood and urine tests for safety assessments and/or determination of eligibility will be performed as indicated in this table and described in the subsections below:

| Chemistry | Hematology | Other | Urinalysis |
|--|---|--|---|
| <u>Screening, Baseline (Day 1), Weeks 16 and 32 (or Early Termination Visit 2):</u> Sodium, potassium, chloride, bicarbonate, glucose (non fasting), Blood Urea Nitrogen (BUN), creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, cholesterol, triglycerides, gamma glutamyltransferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactic dehydrogenase (LDH), alkaline phosphatase, creatine phosphokinase (CPK), and uric acid | <u>Screening, Baseline (Day 1), Weeks 16 and 32 (or Early Termination Visit 2):</u> Complete blood count with differential | <u>Screening only:</u> HbA1c Hepatitis screen (eg, HBsAg, Anti-HCV), HIV test (HIV Ab screen) Urine toxicology screen (eg, for opiates, barbiturates, amphetamines, cocaine, propoxyphene, methadone, phencyclidine, and methaqualone). Serum FSH if applicable <u>Screening, Weeks 24 and 32 (or Early Termination Visits 1 and 2):</u> Serum Pregnancy Test <u>Baseline, Weeks 8 and 16 (Prior to dosing at Dosing Visits):</u> Urine Pregnancy Test <u>Baseline, Weeks 24 and 32 (or Early Termination Visits 1 and 2):</u> Serum and plasma retention samples | <u>Screening only:</u> pH, protein, glucose, ketones, blood, bilirubin, nitrite, specific gravity and leukocytes. Microscopic analysis performed if abnormalities are present on the above components. |
| Does not include PK, PD (NGF), anti-tanezumab antibodies, or biomarkers (refer to sections below for collection details) | | | |

7.3.2.1. Blood Tests

Blood tests for clinical laboratory testing (chemistry, hematology) will be performed. An unscheduled visit(s) may be necessary for follow-up of abnormal test results.

Serum and plasma retention samples will be collected.

See [Section 7.3.2.3.](#) for sample collected for serum pregnancy test and [Section 7.3.2.4.](#) for sample collected for FSH testing.

Blood samples collected for PK, PD (NGF), biomarkers and anti-drug antibody measurements are described in [Sections 7.5.1, 7.5.2, 7.6.](#) and [7.3.9.](#)

7.3.2.2. Urinalysis and Urine Toxicology Screen

Urinalysis and urine toxicology screen will be performed at Screening only.

See [Section 7.3.2.3.](#) for urine pregnancy test.

Urine samples collected for biomarker analyses are described in [Section 7.6.2](#).

7.3.2.3. Pregnancy Tests

For female subjects of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at screening, before investigational product administration at the baseline visit, and at the end of treatment visit. A negative pregnancy result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), and repeated at Visits 8, 16, at the end of the study to confirm the subject has not become pregnant during the study, and at Week 32 (16 weeks after the last dose of investigational product was administered). Pregnancy tests may also be repeated as per request of institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

Qualitative urine pregnancy tests must be sensitive to at least 25 mIU/mL. Qualitative point-of-service urine pregnancy tests will be conducted with the test kit provided by the central laboratory in accordance with instructions provided in its package insert. Subjects who have missed a menstrual period or who show an indeterminant or positive result on the qualitative point-of-service urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test conducted at a certified laboratory).

In the case of a positive human Chorionic Gonadotropin (hCG) test, the subject will be withdrawn from investigational product but may remain in the study.

Refer to [Sections 8.10](#) and [8.10.1](#) for guidance pertaining to exposure during pregnancy and post-natal follow-up.

7.3.2.4. Serum FSH Testing

Female subjects of non-childbearing potential who have not had a hysterectomy or bilateral oophorectomy and who have been amenorrheic at least 1 year with no alternative pathological or physiological cause must undergo serum FSH testing to determine post-menopausal status. A serum FSH level within the laboratory's reference range for post-menopausal females is required. Female subjects who have undergone documented total hysterectomy or bilateral oophorectomy or who have medically confirmed ovarian failure are not of childbearing potential and do not require serum FSH testing.

Female subjects who have been amenorrheic less than 1 year will be considered of childbearing potential.

Female subjects of childbearing potential do not require FSH testing.

7.3.3. Assessment of Pain in Major Joints at Screening with Numeric Pain Scale Rating (NRS)

Average pain in the major joints (shoulders, hips and knees) or any other painful, major joint that will be imaged at Screening, will be assessed by the subject at the Screening Visit with an 11-point Numeric Rating Scale (NRS) ranging from zero (no pain) to 10 (worst possible pain) and captured using IRT.

7.3.4. Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate) will be collected and recorded throughout the study. Vital signs will be collected after the subject has been in a sitting position for at least five minutes at each noted visit.

7.3.4.1. Orthostatic Blood Pressure Measurement

In addition to sitting vital sign measurements, orthostatic blood pressure measurements will be obtained using a standard manual sphygmomanometer. At each of these clinic visits, blood pressure will be assessed in supine and standing positions. Orthostatic blood pressure measurements will be obtained after collection of the sitting vital signs and before any required phlebotomy (and prior to dosing at dosing visits). To minimize chances of orthostatic hypotension related to volume depletion, subjects should be reminded to report for clinic visits well hydrated. In this regard, investigators could consider recommending to subjects that they consume 8 – 16 ounces (240 – 480 mL) of water prior to reporting to the clinic for study visits. All orthostatic blood pressure measurements will be recorded in the IRT system.

Supine blood pressure measurement will be obtained after subjects have been in the supine position for a minimum of 10 minutes. To ensure that a stable supine blood pressure measurement is obtained, at least two systolic and diastolic measurements will be performed. If the replicate systolic and diastolic measurements differ by no more than 10 mmHg and 5 mmHg, respectively, the supine blood pressure will be considered to be stable. The mean of the two stable replicate measures will be considered to represent the baseline supine blood pressure (mean systolic and mean diastolic blood pressure) for that visit. Once the supine blood pressure is considered to be stable, subjects will be asked to assume the standing position. After subjects have been in the standing position for 1 minute and 3 minutes, systolic and diastolic blood pressure will be measured and recorded for both time points. If the measurements do not meet the criteria for orthostatic (postural) hypotension, no further measurements are needed. If either the 1 minute or 3 minute standing BP measurements show decreases meeting the criteria shown in [Table 4](#), the sequence of supine and standing measurements should be repeated up to 2 more times. Refer to [Table 4](#) for the criteria defining orthostatic hypotension and actions that should be taken when orthostatic hypotension criteria are met.

Table 4. ORTHOSTATIC BLOOD PRESSURE CHANGES AND SUBJECT MANAGEMENT

| Mean Supine Systolic Blood Pressure | Decrease in Blood Pressure Defining Orthostatic (postural) Hypotension | Actions |
|-------------------------------------|--|--|
| ≤150 mmHg OR >150 mmHg | ≥20 mmHg systolic or ≥10 mmHg diastolic ≥30 mmHg systolic or ≥15 mmHg diastolic | - Repeat the sequence of measurements (supine, and standing) up to 2 times. If either the 1 minute or 3 minute standing BP meets the orthostatic (postural) hypotension criteria, then that sequence is considered positive. If 2 of 2 or 2 of 3 sequences are positive, then orthostatic hypotension is considered confirmed and an adverse event of orthostatic hypotension will be reported. - Refer to Section 7.4.3. for subject management and dosing guidance. |

Refer to [Section 7.4.3.](#) for guidance on determining which subjects with confirmed orthostatic hypotension will require consultation with a neurologist or cardiologist. Subjects who meet criteria defining orthostatic hypotension at any post-Baseline clinic visit should follow the procedures described in [Section 7.4.3.](#)

7.3.5. 12-Lead Electrocardiogram

A 12-lead ECG will be performed at Screening for determination of ECG-related eligibility. Additional 12-Lead ECGs will be performed at Weeks 24 and 48 (or at Early Termination Visits 1 and 3, as described in [Section 6.4.](#) and [Table 2](#)). Post-Screening ECGs may be collected if needed (for cause), at the discretion of the investigator.

A 12-lead ECG should be recorded after subjects have been resting at least 5 minutes in the supine position in a quiet environment. Digital ECG tracings will be performed using equipment from and analyzed by a central ECG laboratory. All standard intervals (PR, QRS, QT, QTcF, QTcB, RR intervals and heart rate (HR)) will be collected. The QTc interval reading produced by machine will be listed in the data listings. The QT interval will be manually measured by the central laboratory. The cardiologist at the central ECG laboratory reading the ECGs will be blinded regarding investigational product assignment. In the event a clinically significant ECG abnormality is seen at a visit on an ECG obtained for cause (post-treatment), the investigator should consider evaluation of the subject by a cardiologist.

Investigators will also be alerted of subjects with evidence of the following as a potential indicator of sympathetic nervous system dysfunction:

- Significant bradycardia (heart rate of ≤45 beats per minute (BPM) on an ECG, exclusionary at Screening).
- Heart rate decrease from Screening of ≥25% with resulting heart rate <60 BPM.

Investigators should report adverse events of bradycardia for subjects who meet the ECG criteria listed above. Refer to [Section 7.4.3](#) for additional details pertaining to subject evaluation and further dosing with investigational product in subjects with sympathetic function adverse events.

7.3.6. Survey of Autonomic Symptoms (SAS)

The Survey of Autonomic Symptoms (SAS)²² is a validated, easily administered instrument to measure autonomic symptoms that has been proposed to be valuable in assessing neuropathic autonomic symptoms in clinical trials (refer to [Appendix 11](#)).

Subjects will complete the SAS at Screening and Week 24 (or at Early Termination Visits 1 and 3, as described in [Section 6.4](#)). Subjects will enter responses in IRT.

7.3.7. Radiographic Assessments

Scheduled X-rays of each shoulder, hip and knee will be obtained at Screening and at Weeks 24 and 48 (or at Early Termination, as described in [Section 6.4](#)) visits.

Radiographic assessments of other major joints exhibiting signs or symptoms suggestive of osteoarthritis should also be imaged. A major joint is defined as a mobile synovial joint in the limbs such as shoulders, elbows, wrists, hips, knees, ankles and excluding the joints of the toes and hands. Any joint imaged at Screening or other at-risk joints identified during the study period should also be imaged at Week 24 and 48 (or at Early Termination Visit 3, as described in [Section 6.4](#)) visits.

NOTE: It is recommended that the radiographs required at Screening be obtained as soon as possible after the Screening visit to permit central radiology review of the images for determination of subject radiographic eligibility for initial dosing in the study. Subjects will not be permitted to start dosing in the study until the Screening radiographs are reviewed by the Central Reader and eligibility is established. X-rays required for the Week 24 visit may be conducted within 30 days of the visit (ie, before or after the visit). X-rays for the Week 48 visit may be conducted up to 30 days before and, preferably, no more than 14 days after the visit.

For subjects who are discontinued prior to the Week 48 visit, follow-up radiographs of each shoulder, hip and knee (and any other major joint imaged at Screening or other at risk joints identified during the study period) should be performed as soon as possible (refer to [Section 6.4](#)) after the decision to withdraw from the study has been made, provided at least 30 days have passed since the last set of X-rays were collected. A final set of follow-up radiographs of each knee, hip and shoulder (and any other major joint imaged at Screening or other at risk joints identified during the study period) should be obtained 24 weeks (Early Termination Visit 3, [Section 6.4.1.4](#)) after the last dose of SC investigational product was administered.

The X-ray technologists, in addition to their professional training and certifications, will be trained in performing the radiographic protocols for the knees, hips, and shoulders for this study and given approval by Pfizer or its representative to perform study X-rays. To

facilitate reproducibility and accuracy of joint space width measurement in the knees and hips, a standardized subject and joint positioning protocol will be utilized. The Core Imaging Laboratory will be responsible for working with the sites to ensure quality, standardization and reproducibility of the radiographic images/assessments made at the Screening and follow-up time-points. Additional details regarding the required X-rays will be provided in a site imaging manual.

Central radiology readers (Central Readers) will be board certified radiologists or have the international equivalent as musculoskeletal radiologists. The Central Readers will be governed by an imaging atlas and an imaging Charter which includes a specific description of the scope of their responsibilities. Central Readers will review radiology images at Screening for assessment of eligibility (including determination of Kellgren-Lawrence Grade) and identification of exclusionary joint conditions such as rapidly progressive osteoarthritis, atrophic or hypotrophic osteoarthritis, subchondral insufficiency fractures (spontaneous osteonecrosis of the knee [SPONK]), primary osteonecrosis and pathological fractures. After randomization, Central Readers will review radiology images for diagnosis of joint conditions that would warrant further evaluation by the Adjudication Committee such as possible or probable rapidly progressive osteoarthritis, subchondral insufficiency fractures (spontaneous osteonecrosis of the knee [SPONK]), primary osteonecrosis or pathological fracture and subjects undergoing total joint replacement for any reason, all images and other source documentation will be provided to the blinded tanezumab Adjudication Committee for review and adjudication of the event. The Adjudication Committee's assessment of the event will represent the final classification of the event.

7.3.7.1. Radiation Exposure

The International Commission on Radiation Protection (ICRP) has developed and applied the **As Low As Reasonably Achievable (ALARA)** principle in developing guidelines that balance the benefits of radiation exposures against possible risks. This principle states that human exposures to radiation should be “**As Low As Reasonably Achievable**, with economic and social considerations taken into account.”

Within the context of medical and research exposures, this is usually taken to mean that each individual should receive no more radiation than is necessary to obtain reliable information and that no more research participants should be irradiated than is necessary to answer a particular scientific question.

| Radiograph | Annual Effective dose (mSv) |
|------------------------|-----------------------------|
| Knee ²³ | 0.036 mSv |
| Hip ^{24,25} | 2.6 mSv |
| Shoulder ²⁴ | 0.06 mSv |
| TOTAL | 2.696 mSv |

Subject exposure per body part imaged is shown in the table above. The total effective dose per subject in this study is expected to be approximately 2.7 millisievert (mSv).²⁶ This can be compared to the annual effective dose from natural background radiation of approximately 3.0 mSv. In some cases, it is expected that a repeat image of a joint may be necessary due to the quality of the X-ray images.

7.3.8. Neurologic Examination

Neurologic examinations will be performed by a designated physician and assessed for clinically significant changes from Baseline. The examinations will be performed at Screening, Baseline (Day 1), and Weeks 2, 4, 8, 12, 16, 24, 32 and 48 (or at each Early Termination Visit, as described in [Section 6.4.](#) and [Table 2](#)) and the Neuropathy Impairment Score (NIS) will be completed at these time points based on this neurological exam (refer to [Appendix 8](#)). Neurologic examination will assess strength of groups of muscles of the head and neck, upper limbs and lower limbs, deep tendon reflexes and sensation (tactile, vibration, joint position sense and pin prick) of index fingers and great toes in order to complete the NIS. The NIS is a standardized instrument which has been tested in both healthy subjects and subjects with neuropathy and which has been used to evaluate subjects for signs of peripheral neuropathy in clinical trials.²⁷ Investigators and other designated physicians performing the neurologic evaluations are required to attend a training session for neurological exam in order to apply consistency across sites. The neurological exams must be performed in a controlled and consistent manner and by the same examiner when possible.

A neurologic evaluation should be performed by a consulting neurologist if any of the following occurs:

- If an adverse event suggestive of new or worsening peripheral neuropathy or an adverse event of abnormal peripheral sensation (eg, allodynia, burning sensation, carpal tunnel syndrome, dysesthesia, hyperesthesia, hyperpathia, hypoesthesia, neuralgia, neuritis, neuropathy peripheral, paresthesia, peripheral sensory neuropathy, sciatica, sensory disturbance, sensory loss, tarsal tunnel syndrome) is reported as: 1) a serious adverse event or 2) an adverse event which has resulted in the subject being withdrawn from the study, or 3) an adverse event ongoing at the end of the subject's participation in the study, or 4) an adverse event of severe intensity.
- A new or worsened clinically significant abnormality on the neurologic exam should be reported as an adverse event and may result in a neurologic evaluation/consult further to the guidance above.
- A neurological adverse event which is non-neuropathic (eg, stroke, seizure) but which the investigator considers medically important should also result in a neurological consultation.

In these cases, a neurologic evaluation should be obtained as soon as possible after these signs and symptoms are known. The results of the neurological consultation will be recorded on the appropriate CRF and adverse event (if applicable) forms. Adverse events will be reported where applicable as described in [Section 8](#).

7.3.9. Anti-Drug Antibody Testing

Blood samples for the assessment of anti-tanezumab antibody (ADA) against tanezumab (anti-tanezumab antibodies) will be collected and will be analyzed using a validated analytical method in compliance with Pfizer Standard Operating Procedures.

Samples may be used for further evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report.

The shipment address and assay lab contact information will be provided to the investigator.

7.4. Triggered Requirements and Subject-Level Stopping Rules

The following rules will apply to individual subjects at the time of the second and subsequent injections of SC investigational product.

7.4.1. Dysesthesia/Allodynia

Transient, resolved dysesthesia/allodynia: Administer SC investigational product as planned as long as the condition has resolved before the next scheduled dose of SC investigational product.

Unresolved dysesthesia/allodynia: Withhold the SC investigational product for a maximum of 14 days beyond the planned dosing day to allow for resolution of the adverse event. If the dysesthesia/allodynia has not resolved within the 14-day period after the scheduled dosing date, the subject will not receive any additional doses of investigational product and will enter the Early Termination Follow-up period (refer to [Section 6.4](#)).

7.4.2. Hypersensitivity or Injection Site Reactions

If a severe hypersensitivity reaction or severe injection reaction occurs following any administration of SC investigational product, the investigational product should be discontinued immediately and no further administrations of SC investigational product will be allowed. Subjects experiencing these types of reactions will enter the Early Termination Follow-up period (refer to [Section 6.4](#)).

Severe hypersensitivity reactions are defined as those causing anaphylaxis. Severe injection site reactions are defined as those in which ulceration or severe necrosis occurs.

7.4.3. Orthostatic Hypotension and Sympathetic Function Adverse Events

Blood pressure changes meeting the pre-specified criteria for orthostatic hypotension and confirmed as described in [Section 7.3.4.1](#) will be designated as confirmed orthostatic hypotension episode and should be reported as an adverse event whether or not the subject had accompanying symptoms.

Confirmed episodes of orthostatic hypotension: If a confirmed episode of orthostatic hypotension occurs (as defined in [Section 7.3.4.1](#)) it should be reported as an adverse event and the subject should be further evaluated as described below to determine if a neurology or cardiology consultation should be obtained and/or whether further treatment with

investigational product should occur. [Figure 2](#) provides a flow diagram for the process described below.

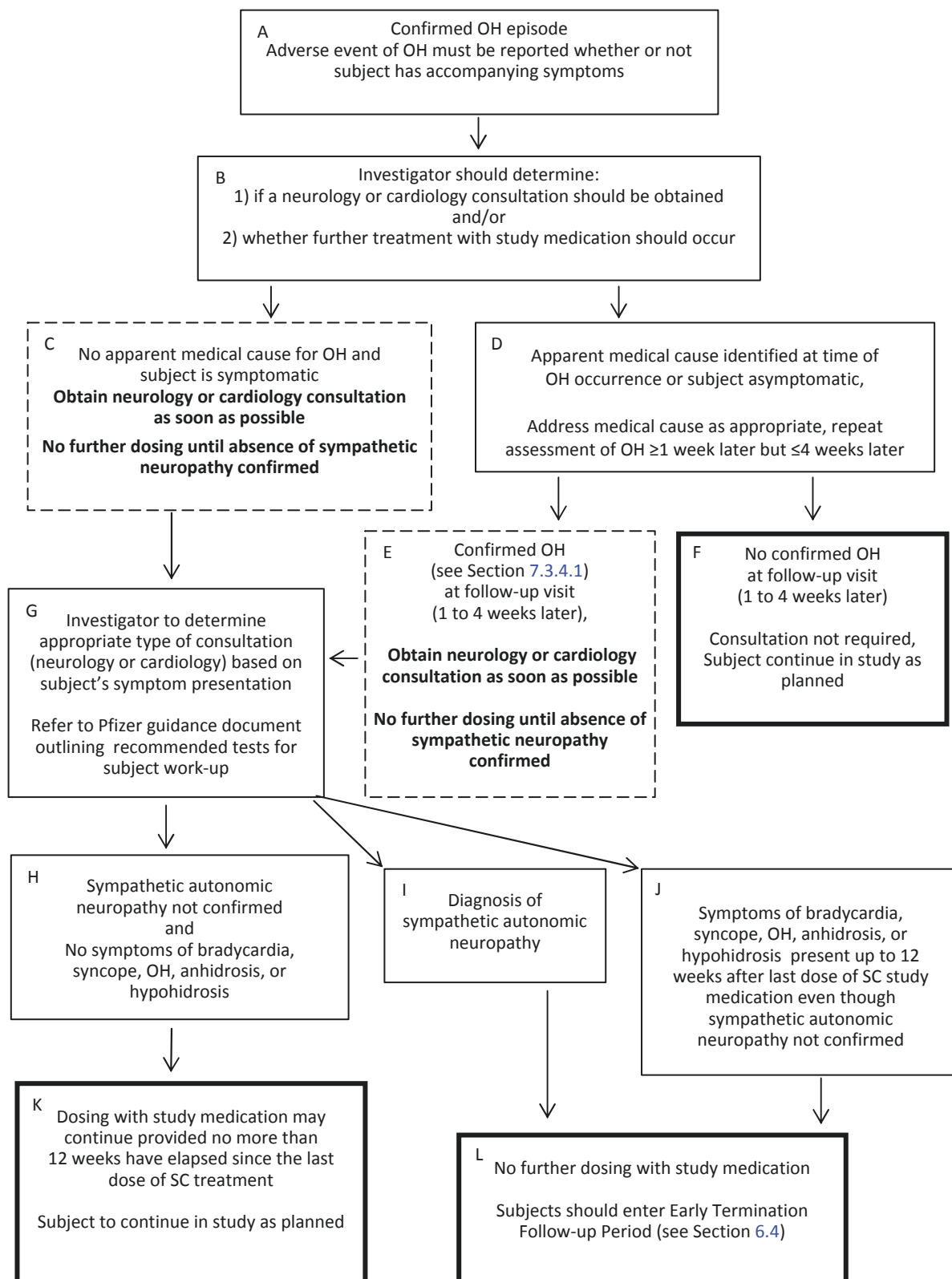
1. If no apparent medical cause (eg, dehydration, illness, medications) is identified at the time the orthostatic hypotension criterion is met and the subject is symptomatic, the subject should be further evaluated for the presence of sympathetic autonomic neuropathy by a cardiologist or neurologist as soon as possible. See “Sympathetic function adverse events” below for decisions regarding subject management and continued dosing with investigational product.
2. If an apparent medical cause is identified at the time the orthostatic hypotension criterion is met or if the subject is asymptomatic, the subject should have a repeat assessment of orthostatic hypotension performed at least 1 week later but not more than 4 weeks later. During this time the investigator should attempt to address the underlying medical cause of the orthostatic hypotension. If confirmed orthostatic hypotension (as defined in [Section 7.3.4.1](#)) is present at the follow-up visit, the subject should be further evaluated for the presence of sympathetic autonomic neuropathy by a cardiologist or neurologist as soon as possible. See “Sympathetic function adverse events” below for decisions regarding subject management and repeat dosing.

Sympathetic function adverse events: Subjects reporting adverse events (any seriousness or severity) with preferred terms of bradycardia (see [Section 7.3.5](#) for ECG criteria for bradycardia), syncope, orthostatic hypotension (as described above and in boxes C and E of flow diagram, [Figure 2](#), anhidrosis or hypohidrosis should be further evaluated for the presence of sympathetic autonomic neuropathy by a cardiologist or neurologist as soon as possible.

The investigator should determine the appropriate type of consultation (neurology or cardiology) depending on the subject’s symptom presentation and the investigator’s assessment as to the specialist best able to evaluate the subject. Pfizer will provide a guidance document which outlines appropriate recommendations regarding tests to consider for subject work-up.

These subjects should not be dosed with SC investigational product until the absence of sympathetic autonomic neuropathy has been confirmed. Subjects who are not deemed to have a sympathetic autonomic neuropathy based on this evaluation can continue the study provided no more than 12 weeks have elapsed since the last dose of SC treatment (Boxes H and K of flow diagram, [Figure 2](#)). However, if the subject is still symptomatic with bradycardia, syncope, orthostatic hypotension, anhidrosis or hypohidrosis up to 12 weeks after the last dose of SC treatment, s/he should not receive additional investigational product, even if a sympathetic autonomic neuropathy has not been confirmed (Boxes J and L of flow diagram, [Figure 2](#)), and will enter the Early Termination Follow up period (refer to [Section 6.4](#)). Subjects found to have a sympathetic autonomic neuropathy (Boxes I and L of flow diagram, [Figure 2](#)) should not receive additional investigational product and will enter the Early Termination Follow up period (refer to [Section 6.4](#)).

Figure 2. Follow-up Procedures for Confirmed Orthostatic Hypotension Events



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7.4.4. Evaluation and Follow-up for Increased, Severe Persistent Joint Pain

Average daily pain in the index joint (hip or knee) will be assessed with an 11-point numeric rating scale (0 to 10) and collected via IRT beginning in the IPAP through Week 24 of the study followed by weekly assessments between Weeks 24 and 48. In addition, on a weekly basis beginning at the Initial Pain Assessment Period and through Week 48 of the study, the subject will also be asked if he/she experienced new onset or increased pain in a major non-index joint (refer to [Section 7.1.1](#)). If a subject responds that he/she has experienced new onset or increased pain in a non-index joint or other major joint (post-baseline), the subject will be asked to rate his/her pain in that joint on the same 11-point numeric rating scale, using a 24-hour recall (refer to [Section 7.1.1](#)) and will be asked to rate his/her pain in that joint for the remainder of the study.

Joint pain scores recorded electronically will be monitored by site staff to identify subjects who have a pattern of severe pain over several days or a rapid increase in pain. Subjects who record increased pain scores of severe intensity (eg, a score of 7-10 out of 10 on a numerical rating scale) in a knee, hip, shoulder or other major joint which is persistent for at least 2 weeks despite treatment with analgesic medication should be evaluated radiographically. An earlier evaluation of the subject can be made at the discretion of the investigator.

At each study visit, systematic site review of the WOMAC Pain Scores, electronically recorded pain scores, and relevant spontaneously reported adverse events will be implemented. In addition, adverse events of joint pain, joint swelling, joint injury/accidents, fractures or worsening of osteoarthritis symptoms in index or non-index joints will be evaluated by the site personnel. An assessment of the subjects' general health and major joints for any changes in their osteoarthritis status will be carried out.

Musculoskeletal physical exam findings, review of reported musculoskeletal adverse events, and in-clinic efficacy assessments will be recorded on specific case report forms for each study visit.

Subjects meeting the criteria for increased severe or persistent pain or with other clinically significant findings based on the assessment of the Investigator are considered to have a joint(s) at risk and must have radiographs (X-rays) of the joint(s) obtained and sent to the Central Reader for assessment. MRI scans will not be required but may be obtained if warranted for diagnostic purposes. If warranted, the subject will be referred to an orthopedic surgeon for evaluation.

Radiographic (and any MRI) images collected as part of follow-up procedures for reports of increased severe or persistent pain or clinically significant findings of the investigator will be assessed by the Central Reader for possible or probable events of rapidly progressive osteoarthritis, subchondral insufficiency fractures (spontaneous osteonecrosis of the knee [SPONK]), primary osteonecrosis, or pathological fracture (refer to [Section 7.4.5](#) and [Section 9.5](#)).

7.4.5. Central Reader and Subject-Level Stopping Criteria for Joint Safety Events

Subjects identified through the measures described above (in [Section 7.4.4](#)) who are determined by the Central Reader to have a possible or probable joint safety event (rapidly progressive osteoarthritis (type-1 or type-2), subchondral insufficiency fractures (spontaneous osteonecrosis of the knee [SPONK]), primary osteonecrosis, or pathological fracture), will be withdrawn from treatment and enter the Early Termination Follow-up period (refer to [Section 6.4](#)).

The Central Reader will review the radiology images on an ongoing basis and provide assessments to the investigator and Pfizer. For subjects who are identified with a possible or probable joint safety event described above and for subjects undergoing total joint replacement for any reason, all images and other source documentation will be provided to the blinded tanezumab Adjudication Committee for review and adjudication of the event. The Adjudication Committee's assessment of the event will represent the final classification of the event (refer to [Appendix 10](#)).

Subjects with adverse event reports of rapidly progressive osteoarthritis (type-1 or type-2), subchondral insufficiency fractures (spontaneous osteonecrosis of the knee [SPONK]), primary osteonecrosis, or pathological fracture, will be withdrawn from treatment and enter the Early Termination Follow-up period (refer to [Section 6.4](#)).

In addition to Subject-Level Stopping Criteria for Joint Safety Events, this study will also employ Protocol-Level Stopping Criteria. Protocol-Level Stopping Criteria for Joint Safety Events are described in [Section 9.6.2](#).

7.4.6. Procedures for Subjects Undergoing Joint Replacement

Subjects who have undergone or plan to undergo total joint replacement or other arthroplasty procedure during the study will be discontinued from investigational product. Follow-up procedures for these subjects are described in [Section 6.4.2](#). In addition, subjects who undergo total knee, hip or shoulder joint replacement surgery during the study (Treatment Period or Follow-up Period) will be followed for 24 weeks after the procedure as part of a separate protocol, provided the subject consents.

7.5. Pharmacokinetic (PK) and Pharmacodynamic (PD)

7.5.1. Plasma for Analysis of Tanezumab

Blood samples for the assessment of the pharmacokinetics of tanezumab will be collected and will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

Samples may be used for further evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report.

The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the trial.

7.5.2. Nerve Growth Factor (NGF) for Pharmacodynamic Analyses

Blood samples will be collected for the assessment of NGF. NGF can exist in different forms including but not limited to NGF bound to drug or not bound to drug, NGF bound to soluble p75, and proNGF. Blood volume collected will limit the number of NGF assessment to 3 to 4 NGF endpoints including a measure of total NGF (sum of all NGF forms). The final set of NGF forms that will be measured will depend on the availability of the analytical assay that can reliably measure the NGF concentration.

NGF samples will be collected at Baseline (Day 1; predose) and Week 8 (predose), Week 24 (predose), Week 32 and Week 48 (or at Early Termination Visits 1 & 2, as described in [Section 6.4](#)).

Instructions regarding sample processing (eg, sample volumes, tube types, storage temperatures) will be provided in the laboratory manual.

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

NGF samples may be used for further evaluation of the bioanalytical methods used for measuring NGF. These data will be used for internal exploratory purposes and will not be included in the clinical report.

The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the study.

7.6. Biomarkers

7.6.1. Serum Biomarkers

Blood samples for the assessment of biomarkers that can be modulated by the osteoarthritis condition will be collected.

If possible, the samples should be obtained at approximately the same time at each study visit to control for diurnal variations in the biomarkers and following a fasting period of at least 8 hours. Fasting status should be recorded on the eCRF.

Currently measurement of 12 biomarkers are planned: CCI

This selection of biomarkers could change due to blood volume limitations and/or assay performance issues. Possibly OA biomarkers different from the ones listed could be added or substituted if considered informative to further understand the osteoarthritis condition.

Instructions regarding sample processing (eg, sample volumes, tube types, storage temperature) will be provided in the laboratory manual.

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

Biomarker samples may be used for further evaluation of the bioanalytical methods. These data will be used for internal exploratory purposes and will not be included in the clinical report.

7.6.2. Urine Biomarkers

For the assessment of the cartilage biomarker CCI [REDACTED] urine samples will be collected. In the Early Termination follow-up, only a sample after 8 weeks should be taken if termination was before Week 8.

The urine sample should be collected from the second void of the day or later. If possible, the samples should be obtained at approximately the same time at each study visit to control for diurnal variations in the biomarkers and following a fasting period of at least 8 hours. Fasting status should be recorded on the eCRF. Sites will provide collection containers and storage instructions for subjects doing home collection.

Instructions regarding sample processing (eg, sample volumes, tube types, storage temperatures) will be provided in the laboratory manual.

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

Biomarker samples may be used for further evaluation of biomarkers other than the ones listed that could improve the understanding of the safety and efficacy profile of tanezumab.

The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the study.

7.7. Banked Biospecimens

7.7.1. Markers of Drug Response

Studying the variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the DNA (deoxyribonucleic acid), RNA (ribonucleic acid), protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of subjects in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/biomarker analyses and retaining them in the Pfizer BioBank makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study.

Providing these biospecimens is a required study activity for study sites and subjects, unless prohibited as such by local regulations or ethics committee decision.

To protect subjects' confidentiality, the banked biospecimens and data generated from them will be coded with the subject's study identification (ID) number. Samples will be kept in a facility accessible only by swiping a badge. Data will be stored on password-protected computer systems. The key between the code and the subject's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will be used only for the purposes described here and in the informed consent document/subject information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also post-marketing research. Subjects can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which event any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Subjects are notified in the informed consent document/subject information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians; nor will they be recorded in the subject's medical record. There is no intention to contact subjects after completion of the clinical study.

A 4 mL blood biospecimen **Prep D1 (K₂ EDTA whole blood collection optimized for DNA analysis)** will be collected at the Baseline (Day 1) visit to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. For example, putative safety biomarkers, drug metabolizing enzyme genes, drug transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

The Banked Biospecimens will be collected from all subjects unless prohibited by local regulations or ethics committee decision. Detailed collection, processing, storage and shipment instructions are provided in the central laboratory manual.

It is possible that the use of these biospecimens may result in commercially viable products. Subjects will be advised in the informed consent document/subject information sheet that they will not be compensated in this event.

7.7.2. Additional Research

Unless prohibited by local regulations, or ethics committee decision, subjects will be asked to indicate on the consent form whether they will allow the banked biospecimens to also be used for the following research:

- Investigations of the disease under study in the clinical trial, and related conditions.
- Biospecimens may be used as controls. This includes use in case-control studies of diseases for which Pfizer is researching drug therapies; use in characterizing the natural variation amongst people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to pharmacogenomics/biomarkers.

Subjects need not provide additional biospecimens for the uses described in this section; the biospecimens specified in the Markers of Drug Response (see [Section 7.7.1.](#)) will be used. Subjects may still participate in the clinical trial if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered adverse events (AEs) regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a Serious Adverse Event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through the end of the safety Follow-up period or through and including 112 calendar days after the subject's last administration of the subcutaneous investigational medication if the subject refuses the protocol defined Follow-up period.

Serious adverse events occurring to a subject after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the Sponsor.

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Adverse events (serious and non-serious) should be recorded on the CRF from the time the subject has taken at least 1 dose of investigational product through the subject's last visit.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EPD);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication

error CRF, which is a specific version of the adverse event (AE) page and on the serious adverse event (SAE) form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an adverse event, as determined by the investigator, the medication error is to be captured on the medication error version of the adverse event (AE) page and, if applicable, any associated AE(s) are captured on an AE CRF page.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

A Serious Adverse Event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

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- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Medical device complaints may meet the SAE reporting requirement criteria (see [Section 8.14.3](#) on Medical Device Complaint Reporting Requirements). An incident is any malfunction (ie, the failure of a device to meet its performance specifications or to perform as intended; performance specifications include all claims made in the labeling for the device) that, directly or indirectly, might lead to or might have led to the death of a subject, or user, or of other persons, or to a serious deterioration in their state of health.

A serious injury that can cause a serious deterioration in state of health can include:

- a life-threatening illness, even if temporary in nature;
- a permanent impairment of a body function or permanent damage to a body structure;
- a condition necessitating medical or surgical intervention to prevent the above 2 bulleted items;
- Examples: clinically relevant increase in the duration of a surgical procedure, a condition that requires hospitalization or significant prolongation of existing hospitalization;
- any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic device test results when used within the manufacturer's instructions for use;
- fetal distress, fetal death, or any congenital abnormality or birth defects.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see [Section 8.14.1](#)).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of

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drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT value ≥ 3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value ≥ 2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤ 2 X ULN or not available.
- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:
 - For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT values ≥ 2 times the baseline values and ≥ 3 X ULN, or ≥ 8 X ULN (whichever is smaller).

Concurrent with

- For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 X ULN **or** if the value reaches ≥ 3 X ULN (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/ international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also

includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

If required on the AE case report forms (CRFs), the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

| | |
|----------|--|
| MILD | Does not interfere with subject's usual function. |
| MODERATE | Interferes to some extent with subject's usual function. |
| SEVERE | Interferes significantly with subject's usual function. |

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (refer to [Section 8.14. Reporting Requirements](#)). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

2. An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
3. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer Drug Safety Unit on an SAE report form and an Exposure During Pregnancy (EDP) Supplemental Form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP Supplemental Form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination and notify Pfizer of the outcome as a follow up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion.
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document in the source document that

the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.10.1. Additional Postnatal Development Follow-up

The Investigator will be asked to assist with collection of assessments of postnatal development as part of a separate protocol. Participation in that protocol is optional and will require that the subject review, agree and sign a separate informed consent document specific to that study, explaining the details of the post-partum follow-up for the subject and the newborn to participate in these assessments of postnatal development.

8.11. Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF, however a copy of the completed SAE report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (See Also [Section 6.4. Subject Withdrawal](#))

Withdrawal due to AEs should be distinguished from withdrawal due to other causes according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject or legally acceptable representative. In addition, each study subject or legally acceptable representative will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as

well as to the initial and follow-up reporting of EDP, exposure via breastfeeding cases and occupational exposure.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications vaccines and/or illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Medical Device Reporting Requirements

All medical device complaints, regardless of whether the medical device complaint is associated with an AE, will be collected on the applicable pages within the CRF. This includes potential incidents or malfunctions associated with the use of a medical device product. An incident or malfunction is an event that might have led to death or serious deterioration in health, or if it occurred again might have led to death or serious deterioration in health.

Pfizer is to be notified of all medical device complaints within 24 hours of the investigator's awareness of the event.

Refer to the Pharmacy Manual for procedures for forwarding medical device complaints not associated with an SAE to Pfizer.

8.14.4. Sponsor's Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

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9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan, which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

A sample size of 270 subjects per treatment group is needed to provide approximately 80% power to achieve statistical significance (at the 5% two-sided level) for the two comparisons of tanezumab 2.5 and 5 mg SC versus placebo, over all three co-primary endpoints. The total sample size will be approximately 810 subjects.

The assumed treatment differences for this calculation come from a combined analysis of Studies A4091011 and A4091014, using an ANCOVA model for the change from Baseline to Week 24 for each of the 3 co-primary endpoints. Imputation for missing data used mixed Last Observation Carried Forward (LOCF) and Baseline Observation Carried Forward (BOCF) matching the reasons for the primary analysis described below in [Section 9.2.1](#). Under this model the difference between tanezumab 2.5 & 5 mg versus placebo were approximately -0.75/-0.77 & -1.01/-1.05 for WOMAC Pain/Physical Function subscales, and -0.25 & -0.34 for the Patient's Global Assessment of Osteoarthritis. The within-group standard deviations were 2.76, 2.63 and 0.94 for WOMAC Pain, WOMAC Physical Function and Patient's Global Assessment of Osteoarthritis, respectively. The correlation of the change from Baseline to Week 24 value for WOMAC Pain versus Physical Function was 0.92. The correlations between Patient's Global Assessment of Osteoarthritis and WOMAC Pain and Physical Function were approximately 0.67.

Using the treatment differences, variability and correlations given above, the sample size of 270 subjects per group would give 80% power to show significant treatment differences using the two-sided 5% significance, for the two tanezumab versus placebo comparisons over all three co-primary efficacy endpoints.

9.2. Efficacy Analysis

9.2.1. Analysis of Primary Endpoint

The primary efficacy population will be the intent to treat (ITT) population, defined as all randomized subjects who received SC investigational product (either tanezumab or matching placebo). The primary analysis will use multiple imputation methods for missing data at Week 24. Details of the multiple imputation procedure are given below. All treatment comparisons will use the two-sided 5% significance level.

The co-primary efficacy endpoints will be analyzed using an ANCOVA model, with model terms for Baseline score, Baseline diary average pain, index joint (knee or hip), highest Kellgren-Lawrence grade, and treatment group, and study site as a random effect. The assessment of significance for the tanezumab SC versus placebo treatment contrasts will use a step-down testing strategy within each of the co-primary efficacy endpoints defined as first

testing tanezumab 5 mg versus placebo, and if statistically significant ($p \leq 0.05$) to then test tanezumab 2.5 mg versus placebo. Finally, a tanezumab treatment group is declared as superior to placebo if the corresponding treatment contrast is significant over all three co-primary endpoints. This testing procedure will maintain the Type I error to 5% or less within each of the co-primary efficacy endpoints, and to less than 5% for all three co-primary efficacy endpoints. An additional (main effects ANCOVA) analysis for each of the co-primary efficacy endpoints will use a per-protocol analysis set, which will exclude subjects who are major protocol deviators.

The primary analysis of the co-primary endpoints will use multiple imputation for missing data, to account for uncertainty around the subject response. The basis for imputing missing values will be dependent on the reasons for missing data. For subjects with missing data due to discontinuation prior to Week 24 for lack of efficacy or for an adverse event or death, imputation will be based on sampling from a normal distribution using a mean value equal to the subject's Baseline efficacy value and the standard deviation (over all treatment groups) of the observed efficacy data at Week 24. For subjects with missing data for any other reason, imputation will be based on sampling from a normal distribution using a mean value equal to the subject's last observed efficacy value and standard deviation (over all treatment groups) of the observed efficacy data at Week 24. Imputed values for the Patient's Global Assessment of Osteoarthritis will be rounded to integer values from 1 to 5. Imputed values for WOMAC Pain and Physical Function will be truncated at 0 and 10. One hundred imputation samples will be used, and the ANCOVA model described above will be used for each imputation dataset. The final results will be calculated using the combined sets of results from each imputation dataset analysis.²

Additional analyses will explore the sensitivity of results to the effect of missing data on the co-primary efficacy endpoints. The first analysis will use the same main effects ANCOVA model as described above, but with LOCF for missing data. The second analysis will use the same main effects ANCOVA model as described above, but with BOCF for missing data. The third analysis will use Mixed Model for Repeated Measurements (MMRM) utilizing all observed data up to and including Week 24.

9.2.2. Analysis of Secondary Endpoints

Secondary efficacy endpoints will examine the change from Baseline to additional timepoints in the WOMAC Pain and Physical Function subscales, and the Patient's Global Assessment of Osteoarthritis, using the multiple imputation for missing data procedure and analysis described above. The change from Baseline in the Patient's Global Assessment of Osteoarthritis to Weeks 2, 4, 8, 12, 16, 24 and 32 will also be analyzed using the Cochran-Mantel-Haenszel test (stratified by the combinations of the two stratification factors). Changes by each level of improvement will be summarized. For this analysis imputation for missing data will used mixed BOCF/LOCF, as well as BOCF and LOCF separately.

Other secondary endpoints include the WOMAC Stiffness subscale, WOMAC Average score and WOMAC Pain subscale items (Pain When Walking on a Flat Surface, and Pain When Going Up or Down Stairs), conducted for the change from Baseline to Weeks 2, 4, 8, 12, 16, 24 and 32. Analysis of Average Pain in the index joint will be conducted for the change from Baseline to Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 28 and 32. The analysis of these endpoints will use the same ANCOVA analysis as described above for the co-primary endpoints, with multiple imputation for missing data.

The OMERACT-OARSI responder index, and subject response endpoints of improvement in the WOMAC Pain ≥ 30 , 50, 70 and 90%, WOMAC Physical Function ≥ 30 , 50, 70 and 90%, and improvement in the Patient's Global Assessment of Osteoarthritis ≥ 2 will be analyzed for change from Baseline to Weeks 2, 4, 8, 12, 16, 24 and 32 using logistic regression for binary data, with model terms for Baseline WOMAC Pain subscale score, Baseline WOMAC Physical Function or Baseline Patient's Global Assessment score, Baseline Diary Average Pain, index joint, Kellgren-Lawrence grade and treatment group. The cumulative distribution of percent change to Weeks 16 and 24 in the WOMAC Pain subscale score and WOMAC Physical Function subscale score will be summarized for the response categories of reductions of $>0\%$, ≥ 10 to 90% (in steps of 10%) and 100% (no reported pain or difficulties at timepoint of interest). Imputation for missing data will use both LOCF and BOCF, where imputation with BOCF will lead to the subject being assessed as a nonresponder for the response endpoint at a particular timepoint. In addition, in order to closely match the primary imputation analysis, a mixed BOCF/LOCF imputation for response endpoints will be used. In this analysis BOCF imputation (ie, a subject would be a nonresponder) would be used for missing data due to discontinuation for reasons of lack of efficacy, adverse event or death up to the timepoint of interest, and LOCF imputation would be used for missing data for any other reason.

The incidence and number of days per week of rescue medication use will be analyzed for Weeks 2, 4, 8, 12, 16, 24 and 32, and the amount of rescue medication use per week will be analyzed for Weeks 2, 4, 8, 12 16 and 24. The incidence of use of rescue medication will be analyzed using logistic regression for binary data, with model terms for Baseline WOMAC Pain subscale score, Baseline Diary Average Pain, index joint, Kellgren-Lawrence grade and treatment group. The number of days and amount of rescue medication (mg dosage of acetaminophen) will be analyzed using the Negative Binomial model, with model terms of Baseline WOMAC Pain subscale score, Baseline Diary Average Pain, index joint, Kellgren-Lawrence grade, and treatment group. Estimated levels of rescue medication use will be shown for each treatment group, and the ratio (with 95% CI) for comparisons versus placebo will be shown. Imputation for missing rescue medication data will use LOCF only. The incidence and number of days of rescue medication use will be summarized up to Week 32, and the amount of rescue medication taken in a week summarized up to Week 24.

The incidence of and time to withdrawal due to lack of efficacy will also be analyzed for discontinuation up to Week 24 (end of treatment period). The time to discontinuation will be analyzed using the log-rank test, with Kaplan-Meier estimates of the time to discontinuation shown for selected percentiles, dependent on the level of discontinuation. The expectation is that these would be the 1st, 2nd, 5th, 10th and 25th percentiles. Other percentiles may be shown

if the level of discontinuation due to lack of efficacy as calculated using Kaplan-Meier procedure is sufficiently large. The analysis of the incidence of discontinuation due to lack of efficacy will be made using logistic regression for binary data, with model terms for baseline WOMAC Pain subscale score, Baseline Diary Average Pain, index joint, Kellgren-Lawrence grade and treatment group.

A table showing number and percentage of subjects will summarize the response for each dimension (item) of the EQ-5D-5L at Baseline and Weeks 8, 16 and 24. These summary tables will be shown by treatment group. In addition, for each treatment and each time point assessed, descriptive statistics (mean, standard deviation, median, number of subjects) will characterize the five-item health status profile on the EQ-5D-5L in terms of the health utility score and the EQ-VAS.

A summary of the change from Baseline to Weeks 8, 16 and 24 in the WPAI:OA impairment scores will be shown by treatment group.

All data from mPRTI will be summarized by visit. Two items of the mPRTI (patient willingness to use drug again; patient preference of drug versus prior treatment) will be analyzed using the Cochran-Mantel-Haenszel test (stratified by the combination of the two stratification factors) at both Weeks 16 and 24. For any analysis using the Cochran-Mantel-Haenszel test, if there are too few subjects in any stratification combination group then an unstratified test will be performed. The HCRU data will be reported as outlined in the Statistical Analysis Plan

All endpoints up to Week 32 will be summarized (where available), and endpoints up to Week 32 will be analyzed. Any efficacy data collected at the Week 32 visit will be excluded from summary and analyses of efficacy with the following exception: Any efficacy data collected at the Week 32 visit for subjects that have discontinued the study early, and the observations are within 10 weeks after the last dose (8 weeks plus a window of 2 weeks) can be included in the efficacy summaries and analyses for the appropriate efficacy window in which the data falls.

9.3. Safety Analysis

Adverse events, concomitant medications, laboratory safety tests, physical and neurological examinations, vital signs, electrocardiogram (ECG), the anti-drug antibody test will be collected for each subject during the study according to the Schedule of Assessments. Standard safety reporting tables will summarize and list the safety data.

Separate adverse event summaries by treatment group for adverse events of decreased sympathetic function will be conducted. More specifically, adverse events with the following preferred terms will be considered to represent adverse events of decreased sympathetic function: Blood pressure orthostatic decreased, bradycardia, dizziness postural, heart rate decreased, orthostatic hypotension, presyncope, sinus bradycardia, syncope, anhidrosis, hypohidrosis, abdominal discomfort, diarrhea, early satiety, fecal incontinence, nausea, vomiting, ejaculation delay, ejaculation disorder, ejaculation failure, hypertonic bladder, micturition urgency, nocturia, urinary frequency, urinary hesitation, urinary

incontinence, respiratory distress and respiratory failure. If necessary, this list of preferred terms may be adjusted for updates made to the MEDICAL DICTIONARY FOR DRUG REGULATORY AFFAIRS (MedDRA) dictionary versions used for reporting.

In addition to summaries of adverse events considered to represent adverse events of decreased sympathetic function noted above, adverse events of syncope, bradycardia, orthostatic hypotension, anhidrosis, or hypohidrosis are designated as adverse events of interest that will be reviewed by the unblinded E-DMC (See [Section 9.6](#)).

Selected adverse events of interest and common adverse events will be summarized using Risk Differences (with 95% confidence intervals) between each tanezumab group and placebo. In addition, significance testing will be performed for adverse events of interest between each tanezumab group and placebo. There will be no multiplicity adjustment for these significance tests.

Incidence of orthostatic hypotension using postural changes in blood pressure, in addition to mean changes in postural blood pressure will be summarized.

The Survey of Autonomic Symptoms (SAS) scores will be summarized by treatment group for the total number of symptoms reported and total impact score. The summary will be shown by visit, and for the change from Baseline.

The Neuropathy Impairment Score (NIS) is the sum of scores over all 37 items from both the Left and Right side. The change from baseline to each post-baseline visit in the NIS, (using LOCF for missing data), and to worst (largest) change from Baseline (over all post-Baseline visits) will be summarized, and analyzed using Cochran-Mantel-Haenszel test (stratified by the combinations of two stratification factors). The NIS data, the neurological consultation data and the conclusion from neurological examination data will be reported. The neurological consultation data will be summarized for all subjects, and for subjects with adverse events of abnormal peripheral sensation, which are described in the adverse event section above. The “conclusion from the neurological examination” data will be summarized for each timepoint, and then a summary of the final assessment over all neurological examinations for each subject.

The incidence of subjects with any of the adjudication outcomes of rapidly progressive osteoarthritis (type 1 and type 2), subchondral insufficiency fracture (or SPONK), primary osteonecrosis, or pathological fracture, and for occurrence of total joint replacement will be shown by number of subjects treated and subject years of exposure (treatment plus follow up periods), for individual treatment groups and differences between tanezumab treatment groups and the placebo treatment group.

The change from Baseline to Weeks 24 and 48 in the Minimum Joint Space Width (JSW) for subjects with Kellgren-Lawrence grades of 2 or 3 in the index joint will be analyzed for subjects with measurements in the knee and hip separately. The percentage of subjects with narrowing over a certain measurement will be shown, over the range of values from 0 (ie, >0 mm, or any narrowing) to ≥ 2 mm, in addition to summary statistics of the mean (with

standard error) and median narrowing. Significant progression of osteoarthritis will be defined using the Bland-Altman method,²⁸ as proposed by OARSI-OMERACT.²⁹

Progression will be defined as 1.96 times the within-subject standard deviation of the change in JSW. The incidence of subjects with JSW narrowing greater than or equal to these values will be shown (with Kellgren-Lawrence grades of 2 or 3 in the index joint), and incidence analyzed using logistic regression for binary data, taking into account study site and baseline JSW as covariates. This summary and analysis will be performed separately for subjects with osteoarthritis of the hip and knee. These analyses will use the Week 24 End of Treatment/Early Termination data and then Week 48 End of Study/Early Termination regardless of the study day of assessment and/or where subjects have discontinued early from the study. In the event of missing data, baseline data will not be carried forward for Radiographic data.

9.3.1. Anti-Tanezumab Antibodies (ADA)

The following assessments of ADA data will be made:

- A listing of the subjects who develop anti-tanezumab antibodies after treatment for each dose, and the proportion of subjects who develop anti-tanezumab will be summarized for each dose.
- The PK profile will be examined for subjects with anti-tanezumab antibodies.

9.4. Analysis of Other Endpoints

Pharmacokinetic Data and Tertiary Endpoints

Tanezumab concentrations will be measured to support the development of a SC population PK model that allows for the prediction of the tanezumab concentration over time in individuals. In addition tanezumab concentrations will be measured to inform the immunogenicity profile of tanezumab.

All other summarization and analysis of tertiary endpoints will be described in the SAP.

9.5. External Adjudication Committee

A blinded Adjudication Committee consisting of external experts in orthopedic surgery, rheumatology, orthopedic pathology, or radiology with expertise in subjects with end stage osteoarthritis and osteonecrosis will be convened. The Adjudication Committee will have written operating procedures and a Charter, including a specific description of the scope of their responsibilities. In general, the Adjudication Committee will be asked to review all possible or probable joint-related safety events identified by the Central Reader (refer to [Section 7.4.5](#)), total joint replacement, as well as investigator reported adverse events of osteonecrosis, rapidly progressive osteoarthritis, subchondral insufficiency fracture (spontaneous osteonecrosis of the knee [SPONK]) or pathologic fracture. Adverse events related to joint safety that the investigator or sponsor considers medically important may also be reviewed by the Adjudication Committee. These will include, but will not be limited to events identified for adjudication by the Central Reader (refer to [Section 7.3.7](#)).

Prior to the Adjudication Committee's review of a given event, the Committee will be provided with blinded, available source documentation of progress reports from the investigator, orthopedic consult reports, operative reports, radiology reports, pathology reports, X-ray images, MRI images, and pathology specimens for review. Copies of all relevant clinical information including the items listed above should be provided to Pfizer or its designee for review by the external Adjudication Committee. Copies of the information should include the study number, site number and subject number, but it should not include the subject's name or initials.

The external E-DMC will be provided with a blinded summary of the Adjudication Committee's review of events after each review meeting.

9.6. Data Monitoring Committee

An independent, E-DMC has been instituted for the tanezumab clinical program. This committee will be composed of at least one rheumatologist, neurologist, statistician, and epidemiologist. The E-DMC will review unblinded safety data including (but not limited to) adverse events and serious adverse events on a regular basis throughout the trial. Adverse events of syncope, bradycardia, orthostatic hypotension, anhidrosis or hypohidrosis along with other adverse events that are possibly related to the sympathetic nervous system will be monitored by the E-DMC during review of unblinded safety data. The E-DMC will have written operating procedures and a Charter, including a specific description of the scope of their responsibilities.

The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the Charter. If the blinded Adjudication Committee identifies adjudicated events of rapidly progressive osteoarthritis type 2, subchondral insufficiency fracture (spontaneous osteonecrosis of the knee [SPONK]), primary osteonecrosis or pathological fracture, occurring at a rate that could trigger the protocol-based stopping criteria, an urgent, ad hoc assessment of the events will be made by the E-DMC.

Any recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate.

Pfizer Standard Operating Procedures regarding periodic safety reviews by the study team and the Tanezumab Risk Management Committee will be followed. This committee will be composed of members inside and outside the immediate study team who will review blinded safety data from individual studies as well as data pooled across the studies on an ongoing basis. A safety review plan will be in place governing the frequency and extent of safety review.

9.6.1. Protocol-Level Rules for Dosing Suspension/Safety Assessment

9.6.1.1. Serious Adverse Events

Tanezumab safety will be reviewed at two levels; blinded data reviews by Pfizer and unblinded reviews by the data safety monitoring board (DMC). The E-DMC will review

unblinded safety data including adverse events and serious adverse events on a regular basis throughout the course of these studies. Pfizer performs blinded review of all serious adverse event data (including those serious adverse events specified below) and a cumulative review on a monthly basis. If blinded review notes a pre-specified serious adverse event occurring at a rate that could trigger the protocol-based dosing suspension rule (ie, at least 3 or more cases of a given pre-specified serious adverse event), an urgent, ad hoc assessment by the E-DMC will be conducted. The E-DMC will determine whether a protocol-based dosing suspension rule should be triggered. At the individual protocol-level, if a given pre-specified serious adverse event is reported in 3 more subjects in any individual tanezumab treatment group than for control group subjects, the protocol-based rule for dosing suspension will be triggered.

The pre-specified serious adverse events are:

- Sudden cardiac death or cardiac death.
- Acute renal failure.
- Anaphylactic shock or severe anaphylactic reaction.
- Neuropathic joint or neuropathic arthropathy (ie, Charcot joint).
- Peripheral neuropathy confirmed with objective findings such as treatment-emergent abnormalities on neurologic examination, nerve conduction abnormalities or biopsy findings consistent with peripheral neuropathy.
- One of the events related to sympathetic dysfunction (orthostatic hypotension, bradycardia, syncope, anhidrosis, or hypohidrosis).

If a protocol-based rule for dosing suspension is triggered, it will result in suspension of further dosing of subjects in the study until a decision is reached regarding whether it is safe to resume dosing in some or all treatment groups or whether the study should be terminated completely. This decision will be made by the Sponsor in consultation with the tanezumab E-DMC.

If the protocol-based stopping rule is triggered, the E-DMC will consider the implications of this action on a program-level basis and formulate a recommendation whether it is safe to continue dosing (for some or all treatment groups) in other ongoing tanezumab clinical studies. Decisions regarding stopping treatment in other ongoing tanezumab clinical studies will be made by the Sponsor in consultation with the E-DMC.

Factors that may be considered in making this decision in relation to serious adverse events or adjudicated clinically significant adverse events include:

- Consideration of relationship of investigational product to the adverse event;

- Consideration of whether similar adverse events are occurring in other tanezumab studies with similar subject populations;
- Dosage of tanezumab (2.5 mg or 5 mg) and distribution of adverse events across tanezumab dose arms;
- Possible differences in the baseline demographics between treatment groups;
- Use of concomitant medications;
- Possible differences in baseline medical history and/or co-morbidities;
- Duration of therapy (0-6 months, 6-12 months).

9.6.1.2. Events consistent with Hy's Law

If two events are reported which are consistent with Hy's Law in tanezumab-treated subjects, irrespective of dose across all ongoing osteoarthritis and chronic low back pain studies, dosing will be temporarily suspended in all studies until the relationship to investigational product is established for the given events which were consistent with Hy's Law. If two events consistent with Hy's Law are considered to be related to treatment with tanezumab or the cause cannot be determined, all dosing in the tanezumab osteoarthritis and chronic low back pain program may be stopped. The E-DMC will determine whether the dosing suspension should be triggered. Subsequently the E-DMC will formulate a recommendation whether all studies should be permanently terminated. Decisions regarding permanently stopping treatment and terminating studies will be made by the Sponsor in consultation with the DMC.

9.6.2. Joint Safety Events

If the blinded Adjudication Committee identifies adjudicated events of rapidly progressive osteoarthritis type 2, subchondral insufficiency fractures (or spontaneous osteonecrosis of the knee [SPONK]), primary osteonecrosis, or pathological fracture occurring at a combined rate that could trigger the protocol-based stopping criteria, an urgent, ad hoc assessment of the events will be made by the External Data Monitoring Committee.

The protocol (or treatment group) stopping rule has three components; the difference in the number of subjects with an adjudicated joint safety event, the exposure-adjusted risk difference (RD) and the exposure adjusted risk ratio (RR) between each tanezumab treatment group and the active comparator group. The exposure-adjusted RD will be calculated as the difference in the ratios of the number of subjects with an adjudicated joint safety event divided by exposure (subject-years) between each tanezumab group and the comparator group. The exposure-adjusted RR will be similarly calculated using the ratio of exposure adjusted event rates (number of subjects with an adjudicated joint safety event divided by exposure) for each tanezumab group relative to the comparator group. The exposure will be calculated as the combined treatment and follow-up periods.

If the RD [REDACTED] (ie, CCI [REDACTED]), and the RR is [REDACTED] and the difference in the number of subjects with adjudicated events joint safety events [REDACTED] for any tanezumab treatment group versus the comparator treatment group, the protocol-based stopping rule will be triggered. If the protocol-based stopping rule is triggered, the E-DMC will formulate a recommendation whether it is safe to continue dosing in some or all treatment groups or whether the study should be terminated completely. This decision will be made by Pfizer in consultation with the E-DMC.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source

documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigative site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board / Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the Investigator File. Copies of IRB/EC approvals should be forwarded to Pfizer. The investigator should also receive approval from the national competent authority before implementing a substantial amendment.

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The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (GCP) (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 and 2008).

NOTE: For Sweden, the study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (GCP) (ICH 1996), and the Declaration of Helsinki¹.

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data, in any reports, publications, or in any other disclosures, except where required by laws.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, address, and other identifiable data will be replaced by a numerical code based on a numbering system provided by Pfizer in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

¹The Declaration of Helsinki (World Medical Association 2013) will be followed except that the study drug (tanezumab) will not be made available to subjects after they have finished the study [NB Tanezumab will not be available to subjects after they have finished the study at all sites].

The investigator must ensure that each study subject, or his or her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's legally acceptable representative, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of Trial in a Member State of the European Union is defined as the last scheduled procedure shown in the Schedule of Activities for the last participant.

13.2. End of Trial in all other Participating Countries

End of trial in all other participating countries is defined as database lock.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of tanezumab at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 1 week. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in subjects that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

[EudraCT](#)

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual subjects has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by the principle investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the Study is part of a multi-center study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, <http://www.icmje.org/index.html#authorship>, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the (Clinical Study Agreement) CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

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Appendix 1. American College of Rheumatology (ACR) Classification Criteria for Osteoarthritis

1986 Osteoarthritis Knee Criteria²⁸

Clinical and radiographic criteria for classification of idiopathic osteoarthritis of the knee.

Meets criteria 1, 2 and 3:

1. Knee pain;
2. Presence of at least 1 of the following 3:
 - Age greater than 50 years.
 - Morning stiffness less than 30 minutes in duration.
 - Crepitus.
3. Presence of osteophytes on X-ray.

Osteoarthritis Hip Criteria³⁰

Combined clinical (history, physical examination, laboratory) and radiographic criteria for osteoarthritis of the hip, traditional format.

1. Hip pain;
2. AND at least 2 of the 3 following features:
 - Erythrocyte sedimentation rate (ESR) less than 20 mm/hour;
 - Radiographic femoral or acetabular osteophytes;
 - Radiographic joint space narrowing (superior, axial, and/or medial).

Because the presence of osteophytes on X-ray is a protocol requirement (defined by a Kellgren-Lawrence X-ray Grade of ≥ 2 in inclusion criteria #3), protocol defined requirement for diagnosis of osteoarthritis of the hip will be the presence of hip pain, presence of osteophytes on x-ray and either an ESR < 20 mm/hour OR joint space narrowing on X-ray.

ESR testing may be conducted at the local laboratory.

Appendix 2. American Society of Anesthesiologists (ASA) Physical Status Classification

ASA Physical Status Classification

The ASA physical status classification system is used for assessing the fitness of patients before surgery. In 1963 the American Society of Anesthesiologists (ASA) adopted the five-category physical status classification system;³¹ a sixth category was later added (<http://www.asahq.org/Home/For-Members/Clinical-Information/ASA-Physical-Status-Classification-System>).

1. A normal healthy patient.
2. A patient with mild systemic disease.
3. A patient with severe systemic disease.
4. A patient with severe systemic disease that is a constant threat to life.
5. A moribund patient who is not expected to survive without the operation.
6. A declared brain-dead patient whose organs are being removed for donor purposes.

Appendix 3. Half-Lives of Prohibited Prior and Concomitant Medications

Half-Lives of NSAIDs and Other Analgesics

Use of analgesics (including marijuana, duloxetine and prescription or over-the-counter (OTC) NSAIDs irrespective of route, eg oral, topical or rectal) except acetaminophen / paracetamol is prohibited through Week 32 of the study beginning 48 hours prior to the start of the IPAP (the seven days prior to Randomization/Baseline (Day 1) or at the period of time prior to the start of the IPAP that is at least 5 times the half-life of the particular analgesic used, whichever is greater. Products containing glucosamine sulfate and chondroitin sulfate should not be initiated during the study; however, subjects who have taken a stable dose of these products for at least 6 months prior to the Initial Pain Assessment Period will be allowed to continue their regimen. Note that a stable regimen of aspirin taken for cardiac prophylaxis at a dose of ≤ 325 mg/day is permitted throughout the study.

These lists are not all-inclusive. The Physician's Desk Reference provides half-life information.

| HALF-LIVES OF NSAIDs AND OTHER ANALGESICS | | |
|--|--------------------------|-------------------------------|
| Analgesic | Half-life (hours) | Minimum Washout Period |
| Aspirin >325 mg/day | 0.25 | 2 days |
| Azapropazone | 15.0 | 4 days |
| Bromfenac | 1.3-3.1 | 2 days |
| Capsaicin (cream, ointments, patches) | 2.0 | 2 days |
| Carprofen | 12.0 | 3 days |
| Celecoxib | 11.0 | 3 days |
| Codeine | 3.5 | 2 days |
| Diclofenac gels | 1.9 | 2 days |
| Diclofenac | 1.1 | 2 days |
| Diclofenac/misoprostol | 2.4-9.0 | 2 days |
| Diffunisal | 13.0 | 3 days |
| Dipyrrone | 2.0-5.0 | 2 days |
| Duloxetine | 8 - 17 | 4 days |
| Etodolac | 6.0 | 2 days |
| Fenbufen | 11.0 | 3 days |
| Fentanyl | Contact study clinician | |
| Fenoprofen | 2.5 | 2 days |
| Flufenamic acid | 1.4 | 2 days |
| Flurbiprofen | 3.8 | 2 days |
| Hydrocodone | 4.5 | 2 days |
| Hydromorphone | 3.0 | 2 days |
| Ibuprofen | 2.1 | 2 days |
| Indomethacin | 4.6 | 2 days |
| Ketoprofen | 1.8 | 2 days |

| HALF-LIVES OF NSAIDs AND OTHER ANALGESICS | | |
|--|--------------|---------|
| Ketorolac | 4.0-9.0 | 2 days |
| Lidocaine patch or EMLA (lidocaine/prilocaine) | 2.0 | 2 days |
| Meclofenamate | 2.0-4.0 | 2 days |
| Mefenamic acid | 2.0 | 2 days |
| Meloxicam | 16.0 to 20.0 | 5 days |
| Meperidine | 3.7 | 2 days |
| Mexiletine | 6.0-17.0 | 4 days |
| Morphine | 2.0 | 2 days |
| Nabumetone | 26.0 | 6 days |
| Naproxen | 14.0 | 3 days |
| Oxaprofen | 40.0-50.0 | 11 days |
| Oxaprozin | 58.0 | 13 days |
| Oxycodone | 3.2 | 2 days |
| Oxycodone CR | 8.0 | 2 days |
| Oxymorphone | 7.3-9.4 | 2 days |
| Phenylbutazone | 68.0 | 15 days |
| Piroxicam | 57.0 | 12 days |
| Pirprofen | 3.8 | 2 days |
| Propoxyphene | 12.0 | 3 days |
| Salicylates | 2.0-15.0 | 4 days |
| Sulindac | 14 | 3 days |
| Suprofen | 2.5 | 2 days |
| Tapentadol | 4 | 2 days |
| Tenoxicam | 60.0 | 13 days |
| Tiaprofenic acid | 3.0 | 2 days |
| Tolmetin | 1.0 | 2 days |
| Tramadol | 5.9 | 2 days |

Corticosteroids The following use of oral or intramuscular corticosteroids is prohibited through Week 32 of the study and: 1) within 30 days prior to the Initial Pain Assessment Period (the seven days prior to Randomization/Baseline) or, 2) at the period of time prior to the start of the Initial Pain Assessment Period that is at least 5 times the half-life of the particular corticosteroid used, whichever is greater or, 3) the anticipated need to start such during the study. Intra-articular injection of corticosteroids within 12 weeks to the index joint or to any other joint within 30 days prior to the Initial Pain Assessment Period is PROHIBITED. Topical, inhaled and intranasal corticosteroids are PERMITTED.

| Corticosteroids | |
|------------------------|--------------------------------|
| Generic | Brand |
| betamethasone | Celestone, Soluspan |
| Cortisone | |
| dexamethasone | Decadron, Dexacort, Turbinaire |

| | |
|--------------------|--|
| fludrocortisone | Florinet |
| hydrocortisone | A-hydroCort, Cortef, Hydrocortone, Solu-Cortef |
| methylprednisolone | Medrol, Solu-Medrol |
| Prednisolone | Orapred, Prelone |
| Prednisone | Cortan, Deltasone, Medicorten |

Hyaluronic Acid

Intra-articular hyaluronic acid injection to the index knee is prohibited within 30 days (or within 18 weeks for long-acting formulations such as Synvisc) of the Initial Pain Assessment Period and throughout the study.

Biologicals

Use of biologicals is prohibited within 3 months of the Initial Pain Assessment Period and during the study.

The following lists are provided for your reference but may not be all-inclusive. Refer to the Physician's Desk Reference for exclusion determination of a particular agent.

| TNFα Inhibitors | |
|--|--------------|
| Generic | Brand |
| Adalimumab | Humira |
| Etanercept | Enbrel |
| Infliximab | Remicade |

Use of live attenuated vaccines (with the exception of Flumist[®] Influenza Virus Vaccine Live, Intranasal or other inhaled live attenuated influenza vaccines and Pneumovax) is prohibited within 3 months of Initial Pain Assessment Period and during the study.

The following lists are provided for your reference but may not be all-inclusive. Refer to the Physician's Desk Reference for exclusion determination of a particular agent.

| Live Attenuated Vaccines | |
|-----------------------------------|-------------------------------------|
| Generic | Brand |
| BCG (for tuberculosis) | Not available in the US |
| Herpes zoster vaccine | Zostavax |
| Influenza, intranasal | FluMist |
| Measles | Attenuvax |
| Measles, Mumps, and Rubella (MMR) | MMR |
| Mumps | Mumpsavax |
| Oral poliovirus vaccine, oral | OPV (no longer available in the US) |

| Live Attenuated Vaccines | |
|---------------------------------|---|
| Generic | Brand |
| Rotavirus, oral | RotaTeq |
| Rubella | Meruvax II |
| Smallpox | Dryvax (Not commercially available in the US) |
| Typhoid, oral | Vivotif Berna |
| Varicella zoster | Varivax |
| Yellow fever | YF-VAX |

Appendix 4. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) NRS3.1 V5 US

English

WOMAC Osteoarthritis Index NRS3.1



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WOMAC NRS 3.1 – English for USA – V5

Page 1 of 6

WOMAC Osteoarthritis Index NRS3.1

CCI



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WOMAC Osteoarthritis Index NRS3.1

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Appendix 5. Patient's Global Assessment of Osteoarthritis

Patient's Global Assessment of Osteoarthritis – Knee

Subjects will answer the following question when the knee is selected as index joint:

Considering all the ways your osteoarthritis in your knee affects you, how are you doing today?

Subjects will rate their condition using the following scale:

| Grade | Description |
|---------------|---|
| 1 – Very Good | Asymptomatic and no limitation of normal activities |
| 2 – Good | Mild symptoms and no limitation of normal activities |
| 3 – Fair | Moderate symptoms and limitation of some normal activities |
| 4 – Poor | Severe symptoms and inability to carry out most normal activities |
| 5 – Very Poor | Very severe symptoms which are intolerable and inability to carry out all normal activities |

Patient's Global Assessment of Osteoarthritis – Hip

Subjects will answer the following question when the hip is selected as index joint:

Considering all the ways your osteoarthritis in your hip affects you, how are you doing today?

Subjects will rate their condition using the following scale:

| Grade | Description |
|---------------|---|
| 1 – Very Good | Asymptomatic and no limitation of normal activities |
| 2 – Good | Mild symptoms and no limitation of normal activities |
| 3 – Fair | Moderate symptoms and limitation of some normal activities |
| 4 – Poor | Severe symptoms and inability to carry out most normal activities |
| 5 – Very Poor | Very severe symptoms which are intolerable and inability to carry out all normal activities |

Appendix 6. Work Productivity and Activity Impairment Questionnaire: Osteoarthritis of the Knee or Hip V2.0 (WPAI:OA)

Work Productivity and Activity Impairment Questionnaire: Osteoarthritis of the Knee or Hip V2.0 (WPAI:OA)

The following questions ask about the effect of your osteoarthritis of the knee or hip on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ____ YES
If NO, check "NO" and skip to question 6.

The next questions are about the past seven days, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your osteoarthritis of the knee or hip? *Include hours you missed on sick days, times you went in late, left early, etc., because of your osteoarthritis of the knee or hip. Do not include time you missed to participate in this study.*

_____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

_____ HOURS

4. During the past seven days, how many hours did you actually work?

_____ HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your osteoarthritis of the knee or hip affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If osteoarthritis of the knee or hip affected your work only a little, choose a low number. Choose a high number if osteoarthritis of the knee or hip affected your work a great deal.

Consider only how much osteoarthritis of the knee or hip affected
productivity while you were working.

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|----|--|
| Osteoarthritis of the knee or hip had no effect on my work | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Osteoarthritis of the knee or hip completely prevented me from working |
|---|---|---|---|---|---|---|---|---|---|---|----|--|

CIRCLE A NUMBER

6. During the past seven days, how much did your osteoarthritis of the knee or hip affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If osteoarthritis of the knee or hip affected your activities only a little, choose a low number. Choose a high number if osteoarthritis of the knee or hip affected your activities a great deal.

Consider only how much osteoarthritis of the knee or hip affected your ability
to do your regular daily activities, other than work at a job.

| | | | | | | | | | | | | |
|--|---|---|---|---|---|---|---|---|---|---|----|---|
| Osteoarthritis of the knee or hip had no effect on my daily activities | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Osteoarthritis of the knee or hip completely prevented me from doing my daily activities |
|--|---|---|---|---|---|---|---|---|---|---|----|---|

CIRCLE A NUMBER

WPAI-OA V2.0 (US English)

Appendix 7. EuroQol 5 Dimension (EQ-5D-5L)

By placing a check mark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems walking ☐
- I have slight problems walking ☐
- I have moderate problems walking ☐
- I have severe problems walking ☐
- I am unable to walk ☐

Self-Care

- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

Pain/Discomfort

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

Anxiety/Depression

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

Continued to next page

We would like to know how good or bad your health is TODAY.

The best health
you can imagine

This scale is numbered from 0 to 100.

100 means the best health you can imagine.

0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below.

100

95

90

85

80

75

70

65

60

55

50

45

40

35

30

25

20

15

10

5

0

Health State: _____

The worst health
you can imagine

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Appendix 8. Neuropathy Impairment Score (NIS) Sample



NEUROPATHY IMPAIRMENT SCORE (NIS)

9123

OBJECTIVE: To provide a single score of neuropathic deficits and subset scores: cranial nerve, muscle weakness, reflexes and sensation. Abnormalities are abstracted from a neurologic examination in which all of the assessments are made.

4

SCORING: The examiner scores deficits by what he (she) considers to be normal considering test, anatomical site, age, gender, height, weight, and physical fitness.

SCORING, MUSCLE WEAKNESS

0 = NORMAL
1 = 25% WEAK
2 = 50% WEAK
3 = 75% WEAK

3.25 = MOVE AGAINST GRAVITY
3.5 = MOVEMENT, GRAVITY ELIMINATED
3.75 = MUSCLE FLICKER, NO MOVEMENT
4 = PARALYSIS

| | RIGHT | | | | | | | | | | LEFT | | | | | | | | | |
|---------------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|--|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|--|
| Cranial Nerves | N/A | 0 | 1 | 2 | 3 | 3.25 | 3.5 | 3.75 | 4 | | N/A | 0 | 1 | 2 | 3 | 3.25 | 3.5 | 3.75 | 4 | |
| 1. 3rd Nerve | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | |
| 2. 6th Nerve | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | |
| 3. Facial weakness | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | |
| 4. Palate weakness | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | |
| 5. Tongue weakness | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | |
| Muscle Weakness | N/A | 0 | 1 | 2 | 3 | 3.25 | 3.5 | 3.75 | 4 | | N/A | 0 | 1 | 2 | 3 | 3.25 | 3.5 | 3.75 | 4 | |
| 6. Respiratory | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | |
| 7. Neck flexion | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | |
| 8. Shoulder abduction | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | |
| 9. Elbow flexion | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | |
| 10. Brachioradialis | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | |
| 11. Elbow extension | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | |
| 12. Wrist flexion | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | |
| 13. Wrist extension | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | |
| 14. Finger flexion | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | |
| 15. Finger spread | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | |
| 16. Thumb abduction | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | |
| | N/A | 0 | 1 | 2 | 3 | 3.25 | 3.5 | 3.75 | 4 | | N/A | 0 | 1 | 2 | 3 | 3.25 | 3.5 | 3.75 | 4 | |
| 17. Hip flexion | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | |
| 18. Hip extension | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | |
| 19. Knee flexion | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | |
| 20. Knee extension | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | |
| 21. Ankle dorsiflexors | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | |
| 22. Ankle plantar flexors | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | |
| 23. Toe extensors | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | |
| 24. Toe flexors | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | |

9123



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Appendix 9. Patient Health Questionnaire (PHQ-9)

Administration of the PHQ-9 is not mandatory but may be used by the investigator to assess the severity of depression. The severity score is the sum of questions 1-9 only. A score of 15 or higher on questions 1 through 9 indicates severe depression. If used the PHQ-9 should be stored in the subject file. The results of this instrument will not be entered into a database, nor will it be analyzed.

PATIENT HEALTH QUESTIONNAIRE (PHQ-9):

| Over the <u>last 2 weeks</u> , how often have you been bothered by the following problems? | Not at all (0) | Several days (1) | More than half the days (2) | Nearly every day (3) |
|--|--------------------------|--------------------------|--------------------------------|--------------------------|
| 1. Little interest or pleasure in doing things | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Feeling down, depressed, or hopeless | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Trouble falling or staying asleep, or sleeping too much | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. Feeling tired or having little energy | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. Poor appetite or overeating | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. Feeling bad about yourself--or that you are a failure or have let yourself or your family down | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. Trouble concentrating on things, such as reading the newspaper or watching television | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 8. Moving or speaking so slowly that other people could have noticed? Or the opposite--being so fidgety or restless that you have been moving around a lot more than usual | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 9. Thoughts that you would be better off dead or of hurting yourself in some way | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Total Score:

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

| Not difficult at all | Somewhat difficult | Very difficult | Extremely difficult |
|--------------------------|--------------------------|--------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

PHQ-9 is adapted from PRIME MD TODAY, developed by Drs Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer Inc. For research information, contact Dr Kroenke at kkroenke@regenstrief.org. Use of the PHQ-9 may only be made in accordance with the Terms of Use available of <http://www.pfizer.com>. Copyright ©1999 Pfizer Inc. All rights reserved. PRIME MD TODAY is a trademark of Pfizer Inc.

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Appendix 10. Adjudication Categories

| Adjudication Category | | Adjudicated Condition |
|-----------------------|--|---|
| 1 | | Primary Osteonecrosis |
| 2 | | Worsening Osteoarthritis |
| 2a | | Rapidly Progressive Osteoarthritis (type-1 or type-2) |
| 2b | | Normal progression of osteoarthritis |
| 2c | | Not enough information to distinguish between rapidly progressive osteoarthritis and normal progression of osteoarthritis |
| 3 | | Subchondral insufficiency fracture |
| 4 | | Pathologic fracture |
| 5 | | Other (with diagnosis specified) |
| 6 | | Not enough information to specify a diagnosis |

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Appendix 11. Survey of Autonomic Symptoms (SAS)²²

| Symptom/health problem | Q1a. Have you had any of the following health symptoms during the past 6 months? | | Q1b. If you answered Yes in Q1a, how much would you say the symptom bothers you? | | | | |
|---|--|---------------------------------|--|--------------------------|--------------------------|--------------------------|--------------------------|
| | | | Not at all (1) | A little (2) | Some (3) | A moderate amount (4) | A lot (5) |
| Do you have lightheadedness? | <input type="checkbox"/> (1) Yes | <input type="checkbox"/> (0) No | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Do you have a dry mouth or dry eyes? | <input type="checkbox"/> (1) Yes | <input type="checkbox"/> (0) No | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Are your feet pale or blue? | <input type="checkbox"/> (1) Yes | <input type="checkbox"/> (0) No | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Are your feet colder than the rest of your body? | <input type="checkbox"/> (1) Yes | <input type="checkbox"/> (0) No | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Is sweating in your feet decreased compared to the rest of your body? | <input type="checkbox"/> (1) Yes | <input type="checkbox"/> (0) No | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Is sweating in your feet decreased or absent (for example, after exercise or during hot weather)? | <input type="checkbox"/> (1) Yes | <input type="checkbox"/> (0) No | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Is sweating in your hands increased compared to the rest of your body? | <input type="checkbox"/> (1) Yes | <input type="checkbox"/> (0) No | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Do you have nausea, vomiting, or bloating after eating a small meal? | <input type="checkbox"/> (1) Yes | <input type="checkbox"/> (0) No | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Do you have persistent diarrhea (more than 3 loose bowel movements per day)? | <input type="checkbox"/> (1) Yes | <input type="checkbox"/> (0) No | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Do you have persistent constipation (less than 1 bowel movement every other day)? | <input type="checkbox"/> (1) Yes | <input type="checkbox"/> (0) No | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Do you have leaking of urine? | <input type="checkbox"/> (1) Yes | <input type="checkbox"/> (0) No | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Do you have difficulty obtaining an erection (men)? | <input type="checkbox"/> (1) Yes | <input type="checkbox"/> (0) No | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Appendix 12. Patient Reported Treatment Impact Assessment-Modified (mPRTI)

PATIENT REPORTED TREATMENT IMPACT ASSESSMENT

Overall, how satisfied are you with the drug that you received in this study?

Please Check (X) ONE only:

- ☐ (5) Extremely satisfied
- ☐ (4) Satisfied
- ☐ (3) Neither satisfied nor dissatisfied
- ☐ (2) Dissatisfied
- ☐ (1) Extremely dissatisfied

PATIENT GLOBAL PREFERENCE ASSESSMENT

Before enrolling in this clinical trial, what is the current or most recent treatment you were receiving for your osteoarthritis pain?

Please Check (X) ONE only:

- ☐ (1) Injectable prescription medicines
- ☐ (2) Prescription medicines taken by mouth
- ☐ (3) Surgery
- ☐ (4) Prescription medicines and surgery
- ☐ (5) No treatment

Overall, do you prefer the drug that you received in this study to the treatment you received before this clinical trial?

Please Check (X) ONE only:

- ☐ (1) Yes, I definitely prefer the drug that I am receiving now
- ☐ (2) I have a slight preference for the drug that I am receiving now
- ☐ (3) I have no preference either way
- ☐ (4) I have a slight preference for my previous treatment
- ☐ (5) No, I definitely prefer my previous treatment

PATIENT WILLINGNESS TO USE DRUG AGAIN ASSESSMENT

In the future, would you be willing to use the same drug that you have received in this study for your osteoarthritis pain?

Please Check (X) ONE only:

- ☐ (1) Yes, I would definitely want to use the same drug again
- ☐ (2) I might want to use the same drug again
- ☐ (3) I am not sure
- ☐ (4) I might not want to use the same drug again
- ☐ (5) No, I definitely would not want to use the same drug again

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Appendix 13. Abbreviations

| This is a list of abbreviations that may or may not be used in the protocol. | |
|--|--|
| Abbreviation | Term |
| Ab | antibody |
| ACR | American College of Rheumatology |
| ADA | anti-drug antibody |
| AE | adverse event |
| AEMPS | Agency on Medicinal Products and Medical Devices |
| ALARA | As Low As Reasonably Achievable |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| ASA | American Society of Anesthesiologists |
| AST | aspartate aminotransferase |
| BID | twice a day |
| BMI | body mass index |
| BOCF | baseline observation carried forward |
| BP | blood pressure |
| BPM | beats per minute |
| BUN | blood urea nitrogen |
| C1M | C-terminal neoepitope of type I collagen |
| CCI | CCI |
| CCI | CCI |
| CPK | creatine phosphokinase |
| CRF | case report form |
| CR | controlled release |
| CRA | Clinical Research Associate |
| CCI | CCI |
| CSA | clinical study agreement |
| CT | computed tomography |
| CTA | clinical trial application |
| CTS | carpal tunnel syndrome |
| CCI | CCI |
| CCI | CCI |
| CYP | cytochrome enzyme system |
| DAAP | United States Food and Drug Administration Division of Analgesia, Anesthetic, and Addiction Products |
| DAI | Dosage and Administration Instructions |
| DNA | deoxyribonucleic acid |
| EC | ethics committee |
| ECG | electrocardiogram |
| E-DMC | External Data Monitoring Committee |

| | |
|--------------|---|
| EDTA | edetic acid (ethylenediaminetetraacetic acid) |
| EIU | exposure in-utero |
| EQ-5D-5L | EuroQol 5 Dimension |
| ER | extended release |
| ESR | erythrocyte sedimentation rate |
| EudraCT | European Clinical Trials Database |
| FDA | Food and Drug Administration (United States) |
| FDAAA | Food and Drug Administration Amendments Act (United States) |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GGT | gamma glutamyltransferase |
| HBsAg | hepatitis B surface antigen |
| CCI | CCI |
| HCV | hepatitis C virus |
| HDPE | high density polyethylene |
| HIV | human immunodeficiency virus |
| HR | heart rate |
| CCI | CCI |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonisation |
| ICRP | International Commission on Radiation Protection |
| CCI | CCI |
| IND | Investigational New Drug application |
| INR | International Normalized Ratio |
| IgG | immunoglobulin G |
| IgG2 | immunoglobulin G Type 2 |
| IPAP | Initial Pain Assessment Period |
| IRB | institutional review board |
| IL | interleukin |
| IL-1 β | Interleukin-1 beta |
| CCI | CCI |
| IRT | interactive response technology |
| ITT | intent to treat |
| IUD | intrauterine device |
| IUS | Intrauterine system |
| IV | intravenous |
| JSW | joint space width |
| LDH | lactate dehydrogenase |
| LFT | liver function test |
| LOCF | Last Observation Carried Forward |
| LSLV | last subject last visit |
| LSMean | least squared mean |
| MedDRA | Medical Dictionary for Drug Regulatory Affairs |
| MHRA | Medicines and Healthcare products Regulatory Agency |

| | |
|---------------|---|
| CCI | CCI |
| MMRM | mixed model for repeated measures |
| mPRTI | Patient Reported Treatment Impact assessment-modified |
| MMR | measles, mumps and rubella |
| mSv | millisievert |
| MVPA | moderate to vigorous physical activity |
| N/A | not applicable |
| NGF | nerve growth factor |
| NGFI | nerve growth factor inhibitor |
| NIS | Neuropathy Impairment Score |
| NNH | number needed to harm |
| NNT | number needed to treat |
| NRS | numeric rating scale |
| NSAID | non-steroidal anti-inflammatory drug |
| NSC | Neuropathy Symptom Change |
| NYHA | New York Heart Association |
| OA | osteoarthritis |
| CC | CCI |
| OMERACT-OARSI | Outcome Measures in Rheumatology – Osteoarthritis Research Society Initiative |
| OTC | over-the-counter |
| PCD | primary completion date |
| PD | pharmacodynamic |
| PEI | Paul Ehrlich Institute |
| PGA | Patient Global Assessment |
| PHQ-9 | Patient Health Questionnaire |
| CCI | CCI |
| PK | pharmacokinetic |
| PO | oral administration (per os) |
| PT | prothrombin time |
| PTH | parathyroid hormone |
| QD | once daily |
| QID | four times a day |
| QT | in electrocardiography, the time corresponding to the beginning of depolarization to repolarization of the ventricles |
| QTc | in electrocardiography, the time corresponding to the beginning of depolarization to repolarization of the ventricles, corrected for heart rate |
| QTcB | QT corrected for heart rate using Bazett's formula |
| QTcF | QT corrected for heart rate using Fridericia's formula |
| RD | risk difference |
| RNA | ribonucleic acid |
| RPOA | rapidly-progressive osteoarthritis |
| RR | risk ratio |

| | |
|---------------|--|
| SAE | serious adverse event |
| SAS | Survey of Autonomic Symptoms |
| SC | subcutaneous |
| SOA | schedule of activities |
| CCI | CCI |
| SPONK | spontaneous osteonecrosis of the knee |
| SRSD | single reference safety document |
| TNF- α | tumor necrosis factor alpha |
| trkA | tropomyosin receptor kinase A |
| ULN | upper limit of normal |
| US | United States |
| VAS | visual analog scale |
| WOMAC | Western Ontario and McMaster University Osteoarthritis Index |
| WPAI:OA | Work Productivity and Activity Impairment Questionnaire: Osteoarthritis |

Appendix 14. Lifestyle Guidelines for Subjects from Sites in Sweden

For sites in Sweden, all female subjects who are of childbearing potential and are sexually active and at risk of pregnancy must agree to use one (1) highly effective method of contraception consistently and correctly for the duration of the active treatment period and for 112 days (16 weeks) after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected the most appropriate method of contraception for the individual subject from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of one of the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the [Schedule of Activities](#) (SOA) and document such conversation in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception methods are discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:³²

1. Established use of hormonal methods of contraception is allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.
Acceptable methods include:
 - combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
 - oral
 - intravaginal
 - transdermal
 - progestogen-only hormonal contraception associated with inhibition of ovulation*:
 - oral
 - injectable
 - implantable

*Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action is not accepted as a highly effective method.

2. Correctly placed intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
3. Bilateral tubal occlusion.
4. Vasectomised partner provided that the partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success.
5. Sexual abstinence, defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Appendix 15. France Appendix

This appendix applies to study sites located in France.

1. GCP Training

Prior to enrollment of any subjects, the investigator and any sub-investigators will complete the Pfizer-provided Good Clinical Practice training course (“Pfizer GCP Training”) or training deemed equivalent by Pfizer. Any investigators who later join the Study will complete the Pfizer GCP Training or equivalent before performing Study-related duties. For studies of applicable duration, the investigator and sub-investigators will complete Pfizer GCP Training or equivalent every three years during the term of the Study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Investigational Product

No subjects or third-party payers will be charged for investigational product.

3. Inspections

The investigator(s) will notify Pfizer or its service provider immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its service provider to prepare the study site for the inspection and will allow Pfizer or its service provider (if not prohibited by law) to be present during the inspection. The study site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its service provider. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its service provider with an opportunity to review and comment on responses to any such findings.

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